NOTES & NOTES

4TH Edition

VOL 1

2025-2026

DR. YOUSIF ABDULLAH HAMAD

MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

FBC

Fareed Book Centre

© Copyright 2025-2026

NOTES AND NOTES

4th Edition

DR. YOUSIF ABDULLAH HAMAD
MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the Copyright Holders.

This book is sold subject to the condition that it shall not, by way of trade or otherwise, be lent, resold, hired out or otherwise circulated without the publisher's prior consent in any form of binding or cover other than that in which it is published and without a similar condition including this condition being imposed on the subsequent purchaser.

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editors, contributors and the publishers have, as far as it is possible, taken care to ensure that the information given in this text is accurate and up-to-date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice. Neither the publisher nor the authors assume any responsibility for any loss or injury and/or damage to person or property arising out of or related to any use of the material contained in this handbook.

Copyright © 2025-2026 All Rights Reserved

Fareed Book Centre
Discover Something New
www.fareedbookcentre.com
156/8, MCB Road, Gulgasht Multan. | 03081401299

SOLE DISTRIBUTOR

Head Office 156/B (Fareed Book Centre) Gulgasht Colony Multan
03081401299
Info@fareedbookcentre.com

Shop No. 9 adjacent Bakhtawar Amir Medical & Dental College Multan
03168081199
Info@fareedbookcentre.com

V-1

Contents

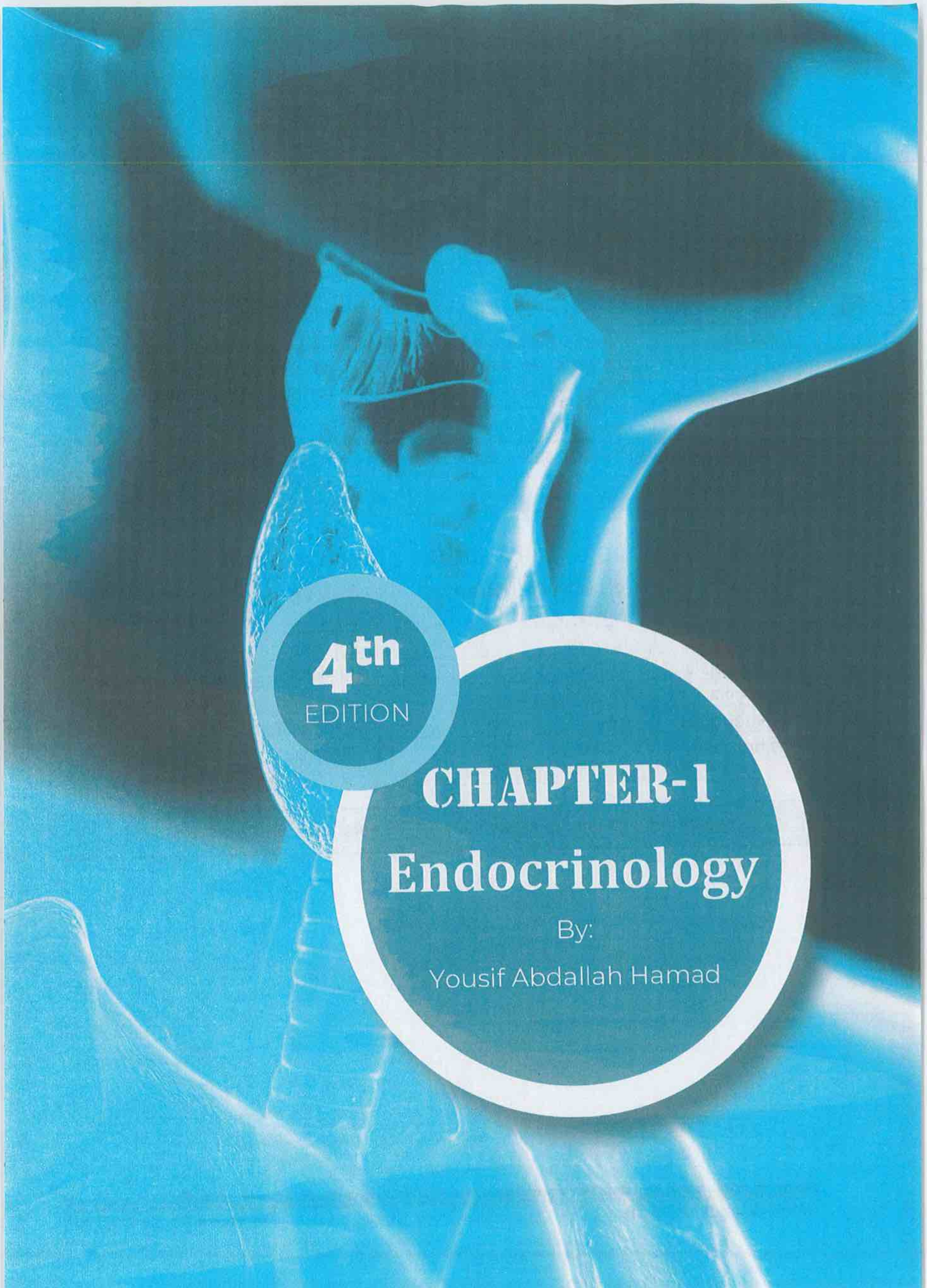
SL	Topic	Page
	Endocrinology	1
1	Pituitary gland anatomy and its clinical significance	2
2	Cell populations of the anterior pituitary gland	2
3	Hypothalamic hormones, action, and clinical significance	3
4	Syndrome of inappropriate ADH secretion (SIADH) ($\uparrow\uparrow$ ADH)	5
5	Diabetes insipidus (DI)	8
6	Hypopituitarism	11
7	Growth Hormone (GH)	12
8	Growth hormone deficiency (GHD)	14
9	Acromegaly	14
10	Pituitary adenoma	16
11	Hyperprolactinaemia	17
12	Hypothyroidism	19
13	Riedel's thyroiditis	20
14	Sick Euthyroid Syndrome (Non-Thyroidal Illness Syndrome)	21
15	Subclinical hypothyroidism	22
16	Post-partum thyroiditis	23
17	Subacute (De Quervain's) thyroiditis	24
18	Subclinical hyperthyroidism	24
19	Thyrotoxicosis	25
20	Amiodarone-induced thyroid dysfunction	26
21	Thyroid eye disease (Graves' Orbitopathy)	27
22	Thyroid storm (crisis)	28
23	Thyroid cancer	29
24	Hypercalcaemia	33
25	Familial hypocalciuric hypercalcaemia (FHH)	35
26	Hypocalcaemia	36
27	Hypomagnesaemia	37
28	Hypermagnesemia	38
29	Vitamin D deficiency	38
30	Hypophosphatasemia	40
31	Hyperphosphataemia	41
32	Hyperparathyroidism	42
33	Hypoparathyroidism	43
34	Osteomalacia	44
35	Osteoporosis	44
36	Primary hyperaldosteronism	51
37	Secondary Hyperaldosteronism	54
38	Adrenal incidentaloma	55
39	Adrenal Hyperandrogenism	56
40	Congenital adrenal hyperplasia (CAH)	57
41	Glucocorticoid remediable aldosteronism (GRA)	61
42	Pseudohyperaldosteronism	61
43	Syndrome of Apparent Mineralocorticoid Excess (SAME)	62
44	Phaeochromocytoma	63
45	Hypoadrenalism	64
46	Corticosteroids Overview	66
47	Cushing's syndrome (Hypercortisolism)	67
48	Metabolic syndrome	71
49	Pre-diabetes or impaired glucose regulation (IGR)	72
50	Diabetes mellitus: Type 1 overview	74
51	Type 1 Diabetes Mellitus: Step-by-Step Management	78
52	Diabetes mellitus: Type 2 overview	79
53	Glycosylated haemoglobin (HbA1c)	82
54	Type 2 Diabetes mellitus: Step-by-Step Management	82
55	Biguanides (metformin)	85
56	Sulphonylureas	86
57	Meglitinides	87

58	Thiazolidinediones (glitazones, insulin sensitizers)	87
59	Insulin	88
60	Diabetic ketoacidosis (DKA)	89
61	Hyperosmolar Hyperglycemic State (HHS)	90
62	Hypoglycaemia	91
63	Hypoglycemia Unawareness	92
64	Diabetic retinopathy	94
65	Diabetic neuropathy	95
66	Diabetic foot	97
67	Diabetic neuropathic arthropathy (Charcot's foot)	98
68	Necrobiosis lipoidica diabeticorum	99
69	Insulinoma	99
70	Glucagonoma	100
71	Maturity-onset diabetes of the young (MODY)	101
72	Latent autoimmune diabetes of adulthood (LADA)	102
73	Mitochondrial diabetes	102
74	Diabetes in pregnancy	103
75	Obesity	104
76	Familial Hyperlipidaemia	106
77	Secondary Hyperlipidemia	108
78	Lipid-lowering agents	110
79	Statins	111
80	Fibrates	114
81	Omega-3 Fatty Acids	114
82	Ezetimibe	114
83	Bempedoic Acid	115
84	PCSK9 Inhibitors	115
85	Inclisiran	116
86	Nicotinic acid (niacin)	116
87	Cholestyramine	117
88	Abetalipoproteinemia	117
89	Gynaecomastia	118
90	Physiological changes during pregnancy – endocrine	119
91	Physiological effects of LH, FSH, and sex hormones	120
92	Dihydrotestosterone (DHT)	121
93	Polycystic ovarian syndrome (PCOS)	125
94	Hypertrichosis	128
95	Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)	128
96	Amenorrhoea	129
97	Turner's syndrome	131
98	Premature ovarian failure	133
99	Menopause	134
100	Hormone replacement therapy (HRT)	135
101	Selective Estrogen Receptor Modulators (SERMs)	137
102	Androgen insensitivity syndrome	137
103	Disorders of sex hormones	138
104	Menstrual cycle	139
105	Delayed puberty	140
106	Gynaecomastia	141
107	Hypogonadism	142
108	Kallman's Syndrome vs Klinefelter's syndrome	146
109	Multiple endocrine neoplasia (MEN) (Autosomal dominant)	148
110	Multiple endocrine neoplasia	150
111	Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)	152

SL	Topic	Page
	Neurology	153
1	Transient ischaemic attack (TIA) and ischaemic stroke	154
2	Carotid artery stenosis	160
3	Specific stroke syndromes	162
4	Haemorrhagic stroke Spontaneous Intracerebral haemorrhage (ICH)	166
5	Subarachnoid haemorrhage (SAH)	168
6	Cerebral venous thrombosis (CVT)	171
7	Cervical vascular dissection	173
8	Localisation of a brain lesion	174
9	Cerebellar lesions	177
10	Localisation of speech problems	177
11	Pupil conditions	178
12	Visual field defects	184
13	Abnormal gait	186
14	Nystagmus	187
15	Chorea and Hemiballism	189
16	Cranial nerves	191
17	Optic nerve palsy	193
18	Oculomotor (third nerve) palsy	194
19	Posterior communicating artery aneurysm (PCA)	195
20	Trigeminal neuralgia	197
21	Abducens (VIth) nerve palsy	198
22	Facial (VII) nerve	199
23	Acoustic Neuroma (Vestibular Schwannoma)	202
24	Labyrinthine Infarction vs Viral Labyrinthine Dysfunction	203
25	Ptosis, Miosis and Mydriasis	204
26	Horner's syndrome	205
27	Bulbar and Pseudobulbar palsy	207
28	Epilepsy	208
29	Tourette Syndrome	212
30	Huntington's disease (HD)	212
31	Parkinsonism	214
32	Parkinson's disease (PD)	214
33	Anti-Parkinson drugs	217
34	Serotonin syndrome and Neuroleptic malignant syndrome (NMS)	219
35	Anticholinergic syndrome (overdose)	219
36	Dystonia	221
37	Botulism	222
38	Parkinson Plus syndromes	222
39	Normal pressure hydrocephalus (NPH)	224
40	Dementia	225
41	Delirium (Acute Confusional State)	228
42	Creutzfeldt-Jakob disease (CJD)	229
43	Transient global amnesia	230
44	Restless legs syndrome (RLS)	231
45	Essential tremor	232
46	Holmes tremor	233
47	Friedreich's Ataxia and Ataxic Telangiectasia	234
48	Motor neuron disease (MND)	236
49	Headache	238
50	Triptans	241
51	Idiopathic intracranial hypertension(IIH)	242
52	Multiple sclerosis (MS)	243
53	Myasthenia gravis (MG)	248
54	Lambert-Eaton myasthenic syndrome (LEMS)	250
55	Neurofibromatosis (NF)	251
56	Tuberous sclerosis (TS)	252
57	Brain Tumors	254
58	Von Hippel-Lindau syndrome (VHL)	255
59	Wernicke's encephalopathy	256
60	Korsakoff syndrome	257
61	Anti-NMDA receptor encephalitis	258
62	Lower back pain	259
63	Transverse Myelitis (TM)	260
64	Metastatic spinal cord compression	261

65	Disc prolapse	262
66	Prolapsed cervical disc (Cervical radiculopathy)	264
67	Lumbosacral plexopathy	265
68	Conus medullaris and cauda equina syndromes	266
69	Subacute combined degeneration of spinal cord (SACDC)	267
70	Syringomyelia	268
71	Anterior spinal artery thrombosis	269
72	Incomplete spinal cord syndromes	270
73	Myotonic dystrophy	271
74	Dystrophinopathies	273
75	Hypokalaemic periodic paralysis and thyrotoxic periodic paralysis	274
76	Neuromyelitis optica (NMO)	275
77	Hearing loss	276
78	Peripheral neuropathy	278
79	Chronic inflammatory demyelinating polyneuropathy (CIDP)	281
80	Neuropathic pain	282
81	Autonomic neuropathy	283
82	Mononeuritis multiplex	284

83	Guillain-Barre syndrome(GPS)	284
84	Radial nerve	285
85	Median nerve	286
86	Carpal tunnel syndrome	288
87	Pronator teres syndrome	288
88	Anterior interosseous syndrome	289
89	Ulnar nerve	289
90	Commonly tested nerves of the lower limbs	290
91	Sciatic nerve palsy	291
92	Femoral nerve palsy	292
93	Meralgia paraesthetica	292
94	Saphenous nerve injury	293
95	Tarsal tunnel syndrome	293
96	Sleep paralysis	294
97	Narcolepsy	295
98	Altitude related disorders	295
99	Complex regional pain syndrome (CRPS)	296
100	Paraneoplastic cerebellum syndrome	296
101	Tricyclic antidepressants overdose	297
102	Selective serotonin reuptake inhibitors (SSRIs)	298
103	Lithium toxicity	298



CHAPTER-1
Endocrinology

By:

Yousif Abdallah Hamad

Pituitary disorders

Pituitary gland anatomy and its clinical significance

Location	Adjacent structure	Clinical significance
Superiorly (5–10 mm above diaphragm sella)	Optic chiasm	Suprasellar extension of pituitary adenoma can lead to bitemporal hemianopia
Laterally	Cavernous sinus (3rd, 4th, 6th cranial nerves, maxillary branch of 5th cranial nerve, and internal carotid artery pass through cavernous sinus)	Parasellar spread of pituitary adenoma or pituitary apoplexy can lead to cranial nerve palsies
Antero-inferiorly	Posterior wall of sphenoid sinus	This is used as standard approach route for trans-sphenoidal surgery

Cell populations of the anterior pituitary gland

Cell type	% of cell types in anterior pituitary	Staining	Location in anterior lobe
Corticotrophs	15–20%	Basophilic	Anteromedial
Gonadotrophs	10–15%	Basophilic	Spread throughout
Lactotrophs	10–25%	Acidophilic	Randomly distributed
Somatotrophs	**50%**	**Acidophilic**	**Lateral part**
Thyrotrophs	<10%	Basophilic	Anteromedial and anterolateral

Somatotrophs constitute around 50% of the anterior pituitary cell population

Hypothalamic hormones, action, and clinical significance

Hypothalamic Hormones: Summary Table

Hormone	Target Organ	Action	Clinical Significance
Corticotropin-Releasing Hormone (CRH)	Anterior pituitary (Corticotrophs)	Stimulates secretion of ACTH (Adrenocorticotropic Hormone)	**Deficiency:** Secondary adrenal insufficiency. **Excess:** Cushing's disease or ectopic ACTH secretion.
Thyrotropin-Releasing Hormone (TRH)	Anterior pituitary (Thyrotrophs)	Stimulates secretion of TSH (Thyroid Stimulating Hormone) and prolactin	**Deficiency:** Hypothyroidism (secondary). **Hyperactivity:** Hyperthyroidism or prolactinoma-associated hyperprolactinaemia.
Gonadotropin-Releasing Hormone (GnRH)	Anterior pituitary (Gonadotrophs)	Stimulates secretion of LH and FSH (Luteinizing Hormone and Follicle-Stimulating Hormone)	**Deficiency:** Hypogonadotropic hypogonadism. **Therapeutic use:** Pulsatile GnRH for infertility; continuous GnRH for androgen-dependent cancers.
Growth Hormone-Releasing Hormone (GHRH)	Anterior pituitary (Somatotrophs)	Stimulates secretion of Growth Hormone (GH)	**Deficiency:** Dwarfism. **Excess:** Gigantism or acromegaly.
Somatostatin (SS)	Anterior pituitary (Somatotrophs), GI tract	Inhibits secretion of GH, TSH, and several gastrointestinal hormones	**Excess:** Suppresses GH and TSH secretion; **therapeutic use** in acromegaly, carcinoid syndrome, and variceal bleeding (e.g., octreotide).
Prolactin-Inhibiting Hormone (Dopamine)	Anterior pituitary (Lactotrophs)	Inhibits secretion of prolactin	**Deficiency:** Hyperprolactinemia (galactorrhoea, amenorrhoea). **Therapeutic use:** Dopamine agonists for prolactinomas (e.g., bromocriptine).
Antidiuretic Hormone (ADH)	Kidney (Collecting ducts)	Promotes water reabsorption by increasing aquaporin channels (V2 receptors); vasoconstriction (V1 receptors)	**Deficiency:** Diabetes insipidus. **Excess:** Syndrome of inappropriate antidiuretic hormone (SIADH).

Hormone	Target Organ	Action	Clinical Significance
Oxytocin	Uterus, mammary glands	Stimulates uterine contraction and milk ejection during breastfeeding	**Clinical use:** Induction of labour. Deficiency: Impaired lactation.

ACTH secretion

Increased by CRH, vasoactive intestinal peptide, catecholamines, and ghrelin.
Decreased by oxytocin, endocannabinoids, and atrial natriuretic peptide.

MRCPI-part-1- January 2018: H/O RTA + rapid pulse and low BP + low Na.

- **What is the most likely explanation for this patient's hyponatremia?**
  ⇨ **Physiologic ADH (vasopressin) secretion**
  - **Hyponatremia that develops after massive hemorrhage is likely dilutional.**
  - When baroreceptors detect decreases in effective arterial volume, such as after massive blood loss, they cause antidiuretic hormone (ADH) to be released from the pituitary gland to increase renal reabsorption of free water, diluting serum sodium levels and causing hyponatremia.
- **What is the appropriate management of this patient?**
  ⇨ **normal saline.**
  - Management of hypovolemic hyponatremia includes volume repletion with normal saline.
  - Correction of hypovolemia removes the stimulus to release ADH, causing free water excretion by the kidneys, which leads to rapid correction of serum sodium levels.
  - volume repletion with normal saline must occur at a slow rate, because rapid correction of hyponatremia can cause central pontine myelinolysis.

May 2016 exam -part-1: Which adaptive mechanism that prevent dying from dehydration?

➔ **Increase of aquaporin-2 in the collecting duct.**

- ADH (vasopressin) → ↑ **aquaporin-2** expression → ↓ water excretion → protect against dehydration

MRCPUK-part-1-january-2018: You are reviewing a patient with a history of cranial diabetes insipidus. He is passing 4–6 litres of urine per day.
Expression of which channel is likely to be decreased most in the collecting duct?

➔ **Aquaporin 2**

- It is found in the apical membranes of collecting duct principal cells.
- Aquaporin 2 gene expression is increased by vasopressin, which leads to increased re-absorption of free water. Expression is therefore downregulated in response to cranial diabetes insipidus.

Syndrome of inappropriate ADH secretion (SIADH) (↑↑ ADH)

Definition

- SIADH is a disorder of **impaired water excretion** caused by the inability to suppress the secretion of antidiuretic hormone (ADH), leading to **euvolaemic, hypotonic hyponatraemia**.

Pathophysiology

- ↑↑ ADH → ↑ water retention → **Euvolemic hyponatraemia (dilutional effects)** → low plasma osmolality + high urine osmolality + ↑urine sodium (above 20 mmol/L)
- Osmotic fluid shifts → Cerebral edema and ↑ intracranial pressure

Causes

Category	Examples
Malignancy	▪ **Small cell lung cancer**
Neurological	▪ Stroke, subarachnoid haemorrhage, subdural haemorrhage ▪ Meningitis/encephalitis/abscess
Infections	▪ Pneumonia, tuberculosis, symptomatic HIV
Drugs	▪ Sulfonylureas , **Thiazides** ▪ **SSRIs**, tricyclics, mono-amine oxidase uptake inhibitors, phenothiazines ▪ **carbamazepine** ▪ Vincristine , vinblastine ▪ Cyclophosphamide, chlorpropamide ▪ **Omeprazole**
Other causes	▪ Surgical procedures ▪ Porphyrias (**SIADH is associated with acute intermittent porphyria)**

Features

- **Symptoms of hyponatremia** (usually asymptomatic until the sodium level falls **below 120 mmol/l)**
  - ⇨ **Mild:** anorexia, nausea, vomiting, headache, muscle cramps (**the earliest symptoms** of acute hyponatremia are **nausea and vomiting**.)
  - ⇨ **Moderate:** muscle weakness, lethargy, confusion
  - ⇨ **Severe:** Seizures, altered consciousness
- **Symptoms of the underlying condition**

Diagnostic criteria: SIADH can only be diagnosed when the following criteria are satisfied:

1. **Euvolemia** (clinically no fluid overload (oedema) or dehydration)
2. **Hyponatremia** (↓ **Plasma sodium <135 mmol/l)** → **hypoosmolality** (↓ Serum osmolality **<280 mOsmol/kg)**
3. ↑ **Urine sodium** (>20 mmol/l) → concentrated urine (**urine osmolality >100 mOsmol/kg)**
4. **Normal thyroid, adrenal**, and **renal** function.

Differential diagnosis

- **Cerebral salt wasting (CSW):** hypovolaemia, hyponatraemia and grossly elevated urine sodium (>100) in patients with head injury. **Treated with replacing fluid and sodium losses**, whereas SIADH is treated with fluid restriction

Management

- **Sever acute symptomatic hyponatraemia:** (who present with neurologic abnormalities, e.g. seizures or ↓ conscious level).
  - ⇨ hypertonic (3%) saline given via continuous infusion
    - Infusion of hypertonic (3%) saline is reserved for patients with acute severe life-threatening hyponatraemia, usually where sodium is less than 120 mmol/l and significant neurological features (i.e. seizures or GCS less than 11).
  - ⇨ correction must be done slowly to avoid precipitating central pontine myelinolysis
    - The sodium serum levels may increase by a maximum of 10 mmol/L within 24 hours or 0.5 mmol/L per hour.
- **Mild acute OR chronic hyponatraemia:** (Na+ ≥ 120 and NO neurological signs)
  - ⇨ **1st line → Fluid restriction** (the initial treatment of choice): **↓daily intake <800 mL/day** except in subarachnoid haemorrhage (as fluid restriction may promote cerebral vasospasm).
  - ⇨ **2nd line** → Demeclocycline (a tetracycline antibiotic →**↓ the responsiveness of the collecting tubule cells to ADH (by inducing nephrogenic diabetes insipidus).** Dose: 300 mg, 3 - 4 times/day). Side effect → Photosensitivity (avoid exposure to sunlight or sun lamps)
  - ⇨ **3rd line** → Tolvaptan (ADH receptor antagonists). Dose: 15 mg once daily, increased up to 60 mg once daily if necessary. Side effects → hepatotoxicity and excessive thirst.

Hyponatraemia **(serum sodium less than 135 mEq/L).**

Prevalence: Occurs in up to 30% of hospitalised patients

Classifications

- **Based on severity:**
  - ⇨ Mild hyponatraemia: serum sodium 130 to 134 mEq/L
  - ⇨ Moderate hyponatraemia: serum sodium 120 to 129 mEq/L
  - ⇨ severe hyponatraemia: serum sodium 120 to 129 mEq/L
- **Based on the time of development:**
  - ⇨ **Acute** hyponatraemia: hyponatraemia that is documented to exist **≤ 48h.**
  - ⇨ **Chronic** hyponatraemia: hyponatraemia that is documented to exist **≥ 48h.**
    - If hyponatraemia cannot be classified, we consider it to be chronic

Mechanisms of causes

1. Water excess
2. Sodium depletion
3. Pseudohyponatraemia: (isotonic hyponatraemia)

Causes of hyponatraemia

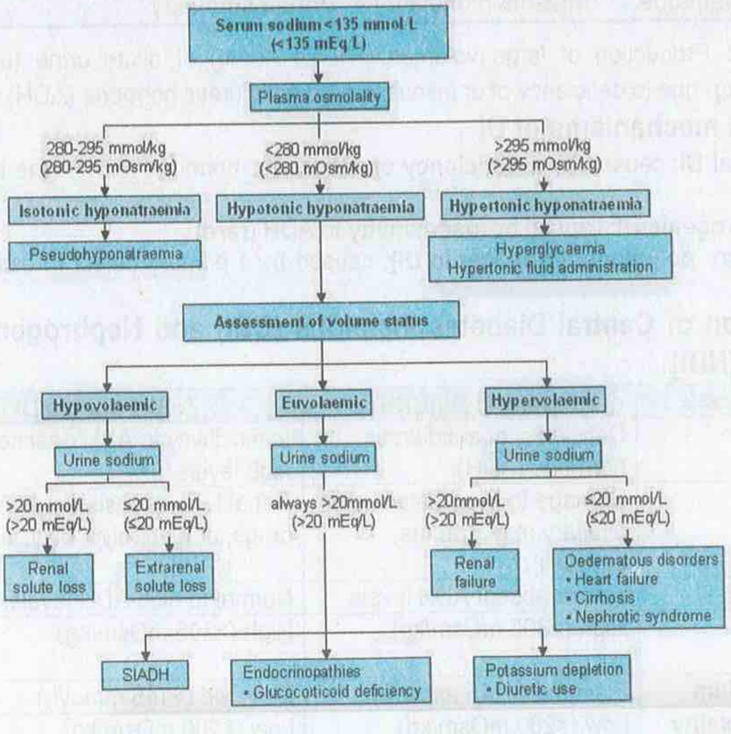
Urinary sodium > 20 mmol/l		Urinary sodium < 20 mmol/l	
Sodium depletion, renal loss (patient often hypovolaemic)	Patient often euvolaemic	Sodium depletion, extra-renal loss (hypovolaemic)	Water excess (patient often hypervolaemic and oedematous)
• diuretics • diuretic stage of renal failure • Addison's	• SIADH (urine osmolality > 500 mmol/kg) • hypothyroidism	• diarrhoea, vomiting, sweating • burns, adenoma of rectum	• secondary hyperaldosteronism: heart failure, cirrhosis • reduced GFR: renal failure • IV dextrose, • psychogenic polydipsia

Features

- Fatigue, Muscle weakness
- Gait disturbance, Falls
- Cerebral oedema → Disorientation, Seizures

Investigations

- Spot (random) Urinary sodium and osmolarity (urinary sodium may be misleading in renal impairment or diuretic therapy).
- Thiazide diuretic abuse → hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hypomagnesemia, hypercalcemia, hyperuricemia and hyperglycaemia.



Management

- **Hypovolaemic hyponatraemia** (↑urea suggests dehydration): **rehydration with sodium chloride 0.9%**. avoid rapid Na correction (aim ≤ **10** mEq/L per day) to reduce the risk of central pontine myelinolysis.
- **Euvolaemic hyponatraemia:** treat the underlying cause where possible in SIADH PLUS fluid restriction, demeclocycline or tolvaptan to inhibit the action of antidiuretic hormone.
- **Hypervolaemic hyponatraemia:** treat the underlying cause (e.g. cardiac failure), fluid and salt restriction, diuretics
- **Acute (< 48 hours) or chronic (> 48 hours) hyponatraemia with any symptoms of intracranial pressure** (seizures, coma, respiratory arrest, headache, nausea, vomiting, tremors, gait or movement disturbances, or confusion): 100 mL bolus of **3% hypertonic saline**, followed if symptoms persist, with up to two additional 100 mL doses (to a total dose of 300 mL) over 30 minutes.
- **Goal of correction**
  - ⇨ **In asymptomatic or mild symptomatic severe hyponatremia** (serum sodium of <120 mEq/L): raise the serum sodium by 4 to 6 mEq/L in a 24-hour period (maximum correction rate 8 mEq/L/24-hour).
  - ⇨ **In patients with severe symptoms (seizures or coma):** 4 to 6 mEq/L, over ≤ 6 hours.

Diabetes insipidus (DI)

Diabetes insipidus → ↑ plasma osmolality + ↓urine osmolality

Definition: Production of large volumes (>3L/24 hours) of dilute urine (urine osmolality <300mosm/kg) due to deficiency of or insensitivity to antidiuretic hormone (ADH).

Types and mechanisms of DI

1. **Cranial DI**: caused by a **deficiency** of antidiuretic hormone (ADH) (**the most common type**)
2. **Nephrogenic DI**: caused by **insensitivity** to ADH (**rare**)
3. **Primary polydipsia (dipsogenic DI)**: caused by a primary defect in osmoregulation of thirst.

Comparison of Central Diabetes Insipidus (CDI) and Nephrogenic Diabetes Insipidus (NDI)

Feature	Central DI (CDI)	Nephrogenic DI (NDI)
Definition	Deficiency of antidiuretic hormone (ADH).	Insensitivity to ADH despite normal or high levels.
Cause	Damage to hypothalamus or pituitary (e.g., trauma, tumours).	Renal tubules resistant to ADH (genetic, drugs, or electrolyte disturbances).
ADH Levels	Low or absent ADH levels.	Normal to high ADH levels.
Plasma Osmolality	High (>305 mOsm/kg).	High (>305 mOsm/kg).
Serum Sodium	Elevated (>145 mmol/L).	Elevated (>145 mmol/L).
Urine Osmolality	Low (<200 mOsm/kg).	Low (<200 mOsm/kg).

Feature	Central DI (CDI)	Nephrogenic DI (NDI)
Water Deprivation Test	Responds to desmopressin with an increase in urine osmolality.	No significant response to desmopressin.
Causes	Trauma, neurosurgery, pituitary tumours, infection, stroke.	Genetic mutations, lithium toxicity, hypercalcaemia, hypokalaemia, tubulo-interstitial disease.
Response to Desmopressin	Good response: Normalises plasma and urine osmolality.	Poor or no response: Urine osmolality remains low.
Treatment	Desmopressin (oral or intranasal).	Address underlying cause (e.g., stop lithium). Thiazide diuretics, NSAIDs, and amiloride may help.
Example Drug Therapy	Desmopressin 100–200 micrograms, 3 times daily.	Amiloride for lithium-induced NDI, thiazides to reduce polyuria.

Diagnosis

- **Rule out other causes of polyuria**
  - ⇨ Diuretics, lithium, caffeine & alcohol
  - ⇨ Diabetes mellitus, heart failure, renal failure
  - ⇨ Hypercalcaemia, hyperthyroidism, hypokalaemia
- **Confirm polyurea:** measure a 24-hour urine output (normal <3L).
- **Initial tests**
  - ⇨ High **plasma osmolality >305 mOsmol/kg**. Serum Na >145 mmol/L.
  - ⇨ Low **urine osmolality <200 mOsm/kg**. Urinary Na 20-60 mmol/L. urinary specific gravity <1.005.
- **Confirmatory test**: Water deprivation test **with response to desmopressin** (the patient is deprived of fluids for up to 8 hours or 5% loss of body weight, then desmopressin 2 micrograms IM given).
  - ⇨ ↓ urine osmolality and ↑ serum osmolality, **CORRECTED** (without desmopressin) → **DI ruled out,** and **primary polydipsia** confirmed.
  - ⇨ ↓ urine osmolality and ↑ serum osmolality, **CORRECTED** by adding Desmopressin (plasma osmolality normalises and urine osmolality rises) → **CDI**
  - ⇨ **NDI** → ↓urine osmolality and ↑ serum osmolality, with **no significant response to desmopressin → NDI**
- **CT scan or MRI of the head:** If CDI is diagnosed, to rule out brain tumours

> In suspected DI the most appropriate next investigation is → Urine and plasma osmolality (non-invasive first step)

Management of Diabetes Insipidus (DI)

Type	Primary Treatment	Dose	Additional Management
Central Diabetes Insipidus (CDI)	**Desmopressin (DDAVP)**	- Oral: 100–200 mcg 2-3x/day - Intranasal: 10–20 mcg/spray - Sublingual: 120 mcg 3x/day - IV/IM: 1–4 mcg/day	- Encourage drinking only when thirsty - Adjust water intake to avoid fluid overload
Nephrogenic Diabetes Insipidus (NDI)	**Thiazide diuretics (e.g., Hydrochlorothiazide)** **Amiloride** **NSAIDs (e.g., Indomethacin)**	- Hydrochlorothiazide: 25–50 mg daily - Amiloride: 5–10 mg daily - Indomethacin: 50–100 mg daily	- Stop offending drugs (e.g., lithium) - Limit salt and protein intake
Gestational DI	**Desmopressin**	Same as CDI doses	- Avoid if due to a defective thirst mechanism to prevent water intoxication
Dipsogenic DI (Primary Polydipsia)	No specific pharmacologic treatment	N/A	- Behavioral strategies to manage water intake

Drug-induced Nephrogenic DI: **lithium, cidofovir, amphotericin B, demeclocycline, ifosfamide, ofloxacin, orlistat, and didanosine.**

Nephrogenic DI is the most common adverse effect of lithium and occurs in up to 40% of patients.

Hypokalaemia is a rare cause of polyuria and polydipsia

If there is hypovolaemic hypernatraemia ((hypotension, tachycardia, poor skin turgor)): **The first step is** to restore volume with isotonic fluids (0.9% saline).

Hypopituitarism

Definition: Deficiency of one or more anterior pituitary hormones.

Features (depends on which hormone is deficient).

- **GH deficiency** → growth retardation (in children →short stature), (**in adults** → **tiredness, weight gain**), ↓ bone density, muscle atrophy, hypercholesterolemia.
- **Prolactin deficiency** → lactation failure following delivery
- **FSH/LH deficiency** → hypogonadotropic hypogonadism (secondary hypogonadism)
- **TSH deficiency** → Secondary hypothyroidism → weight gain, cold intolerance, lethargy, constipation, dry skin.
- **ACTH deficiency** → Secondary adrenal insufficiency → weight loss, weakness, **Postural hypotension**, chronic hyponatremia, hypoglycemia (in contrast to primary adrenal insufficiency, it does not cause hyperpigmentation, salt wasting, low volume, and hyperkalemia because it does not induce aldosterone deficiency).
- **FSH/LH deficiency** → hypogonadotropic (secondary) hypogonadism.
  - ⇨ **Women** → primary amenorrhea (delayed puberty), secondary amenorrhea, irregular menstrual cycles, infertility. **The presence of regular menstrual cycles in women rules out hypogonadism.**
  - ⇨ **Men** → delayed puberty, loss of libido, infertility, testicular atrophy.
- **Prolactin deficiency** → inability to lactate after delivery
- **Intrasellar/parasellar masses** (e.g., pituitary macroadenomas, craniopharyngiomas) can manifest with headache, visual field defects (bitemporal hemianopsia), and/or diplopia
- **Pituitary apoplexy** → Severe headache, bilateral hemianopia, diplopia (due to damage to CN III), sudden hypotension.
- **Houssay phenomenon:** Amelioration of diabetes mellitus in patients with hypopituitarism due to reduction in counter-regulatory hormones.
- Hypopituitarism becomes symptomatic when more than 80% of pituitary cells are damaged.

Causes

- **Intrasellar/parasellar masses**: **Nonsecretory pituitary macroadenomas (≥ 10 mm in diameter) are the most common cause (~ 40% of cases).** Less common: internal carotid artery aneurysms, meningiomas, craniopharyngiomas,
- **Pituitary apoplexy** → acute hypocortisolism and hypothyroidism, → sudden hypotension and hypovolemic shock
- **Sheehan syndrome:** postpartum necrosis of the pituitary gland. Usually occurs following postpartum haemorrhage but can also occur even without clinical evidence of haemorrhage.
- **Traumatic brain injury** (especially around the skull base)
- **Infiltration** of the pituitary and/or hypothalamus: Hemochromatosis, Sarcoidosis or Infections (meningitis, TB)
- **Empty Sella syndrome**
- **Iatrogenic** (Hypophysectomy, Pituitary irradiation)
- **Congenital:** deficiency of hypothalamic hormones: GnRH deficiency (Kallman syndrome)

Investigations

- **Central/secondary adrenal insufficiency:** low morning cortisol level + Low to normal ACTH
- **Growth hormone deficiency**
  - ⇨ **Serum insulin-like growth factor-1 (IGF-1).** It may be normal in up to half of GHD.
  - ⇨ **If IGF-1 is equivocal, a subnormal GH response to a provocative test will confirm the diagnosis. Insulin stress test (the gold standard dynamic test)**
    - **Method:** a weight-based dose of intravenous insulin to achieve a hypoglycaemia level below 2.2 mol/l.
    - **Interpretation:** With normal pituitary function, GH and cortisol should rise.
    - **Contraindications:** epilepsy, ischaemic heart disease and adrenal insufficiency.
- **Thyroid function tests** → secondary hypothyroidism:**↓ or normal TSH with ↓ serum-free T4 and ↓ serum-free T3**
- **Gonadotropin deficiency**
  - ⇨ **In males:** low serum **testosterone** (total testosterone in non-obese or free testosterone if he is obese) at 8 to 10 AM + **non-elevated LH.**
  - ⇨ **In females of premenopausal age who have amenorrhea** → low estradiol + non-elevated FSH.
- **MRI brain**

Management: pituitary hormone replacement + treat the underlying cause

- **Hydrocortisone:**
  - ⇨ **Should be started first** (before thyroxine because levothyroxine increases cortisol clearance and may precipitate an adrenal crisis). Fludrocortisone is only necessary if the patient is unable to maintain normal BP
  - ⇨ Thrice-daily regimens (10mg on waking, 5mg at lunchtime, and 5mg early evening) or twice-daily regimens (15– 20mg/ day and the highest dose to be taken in the morning at awakening)
- **Thyroxine:** (after commencing hydrocortisone): 100– 150 micrograms/ day
- **GH therapy:** 0.2– 0.6mg/ day for adults (0.4– 1.0IU)
- **Testosterone: to prevent the progression of bone loss**

Growth Hormone (GH)

Secretion

- Hypothalamus secretes **Growth Hormone-Releasing Hormone (GHRH)** → stimulates **somatotrophs** in the anterior pituitary → release of GH.
- GH secretion is **pulsatile**, with peak levels occurring around midnight during sleep.
- GHRH stimulates GH release via **cAMP** and **IP3/Ca^{2+}** pathways.

Signaling Pathway

- GH acts through a **tyrosine kinase receptor** mechanism.

Mechanism of Action

1. **Direct Actions** (via tyrosine kinase receptor):
    - ↓ Glucose uptake into cells → ↑ Blood glucose & insulin resistance.
    - ↑ Lipolysis.
    - ↑ Protein synthesis in muscles.
    - ↑ Amino acid uptake.
2. **Indirect Actions** (via Insulin-Like Growth Factor-1 (IGF-1), mainly from the liver):
    - Stimulates growth.
    - Exerts anabolic effects.

Note: GH counters the effects of **insulin** on glucose and lipid metabolism but shares insulin's **anabolic effects** on protein synthesis.

Regulation of GH Secretion

Increased GH Secretion	Decreased GH Secretion
Deep sleep	Somatostatin
Fasting → Hypoglycaemia	Beta-adrenergic activity
Alpha-adrenergic activity	Hyperglycaemia (initially)
Stress	Obesity
Exercise	Free fatty acids
Ghrelin (hunger hormone)	Hypothyroidism
Amino acids (arginine)	IGF-1
Sex steroids (oestrogen/testosterone)	Pregnancy
Puberty	Increased age
CKD	Chronic glucocorticoid therapy
Thyroid hormone (thyroxine)	Glucose
Short-term glucocorticoid exposure	

Clinical Considerations

- **Type 1 Diabetes Mellitus (DM):** GH levels are increased.
- **Type 2 DM:** GH levels may be increased, normal, or decreased.
- **Malnutrition:** ↑ GH levels with ↓ IGF-1 levels.
- **Poorly Controlled Diabetes:** ↑ GH levels with normal or low IGF-1 levels (dissociation).

Conditions Associated with GH Disorders

1. **GH Deficiency:** Short stature.
2. **GH Excess:** Acromegaly.

Key Points for MRCP

1. GH secretion is pulsatile and regulated by both stimulatory (e.g., GHRH, ghrelin) and inhibitory (e.g., somatostatin, IGF-1) factors.
2. GH acts directly via tyrosine kinase receptors and indirectly via IGF-1 to stimulate growth and metabolism.
3. GH counters insulin's effects on glucose and lipids while supporting its anabolic effects on protein.
4. GH levels rise in malnutrition and poorly controlled diabetes but may vary in Type 2 DM.

Growth hormone deficiency (GHD)

Category	Details
Causes	- **Pituitary tumours** or their treatment (e.g., surgery, cranial irradiation) - Other causes of hypopituitarism
Features	**Infants:** Hypoglycaemia, micropenis **Children:** Growth failure, premature epiphyseal fusion **Adults:** Increased fat mass, reduced lean mass, low bone mineral density, dry skin, reduced energy and QoL, increased cardiovascular risk, insulin resistance, and dyslipidaemia (↑LDL)
Diagnosis	- **Serum IGF-1 levels:** May be normal in up to 50% of cases - **Dynamic GH secretion tests**: Insulin Tolerance Test (ITT) is the gold standard. GH response <9 mU/L (3 ng/ml) confirms GHD. False positives can occur with obesity. Contraindicated in seizures, IHD, abnormal ECG, or elderly. Alternative: Arginine-GHRH or Glucagon-GHRH tests.
Treatment	**Subcutaneous recombinant human GH injections** administered if: 1. Severe GH deficiency (peak GH response <9 mU/L) 2. Impaired QoL (QoL-AGHDA score ≥11) 3. Treatment of other pituitary hormone deficiencies
Adverse Effects of GH replacement	- Sodium and water retention (weight gain, carpal tunnel syndrome) - Hyperinsulinaemia - Arthralgia and myalgia - Benign intracranial hypertension (resolves when treatment stops)
Contraindications for GH	- Active malignancy - Benign intracranial hypertension - Proliferative/pre-proliferative retinopathy in diabetes mellitus

Acromegaly

Definition

- Acromegaly is a condition caused by excess growth hormone (GH).

Epidemiology

- Rare, with most cases diagnosed between ages **40–60 years.**

Causes

- **Pituitary adenoma** (95%)
- **Ectopic GHRH or GH** production from tumours (e.g., pancreatic).

Clinical Features

Symptom	Details
Neurological	Headaches, visual field loss, diplopia (cranial nerve palsy).
Face and Mouth	Coarse facial features, prognathism, large tongue (sleep apnoea), bitemporal hemianopia.
Hands and Feet	Spade-like hands, increased shoe size.
Sweating	Excessive sweating due to sweat gland hypertrophy.

Complications

- **Hypertension** (40%)
- **Insulin resistance and diabetes mellitus** (20–40%)
- **Sleep apnoea**: Soft tissue swelling in nasopharyngeal region
- **Cardiovascular diseases**: Ischaemic heart disease, cardiomyopathy, heart failure
- **Osteoarthritis, arthralgia, pseudogout**
- **Carpal tunnel syndrome**: Positive Tinel's sign
- **Colonic polyps and carcinoma risk**
- **Multiple Endocrine Neoplasia type 1 (MEN-1)**: Hyperparathyroidism, hypercalcaemia

Investigations

Test	Details
IGF-1 levels	Screening test; normal levels rule out acromegaly.
OGTT with GH measurement	Gold standard; lack of GH suppression (<1 µg/L) confirms diagnosis.
Pituitary MRI	Detects adenoma in 98% of cases.
GHRH and radiological imaging	To detect ectopic GHRH-secreting tumours if no pituitary adenoma is found.
Additional labs	Hypercalcaemia, hyperphosphataemia, and hyperprolactinaemia in some cases.

Management

Treatment	Details
Surgery	Transsphenoidal adenomectomy: First-line therapy. Success rates: >85% for microadenomas, 40-50% for macroadenomas.
Somatostatin analogues	Octreotide, lanreotide: Used when surgery is not possible or unsuccessful. IM every 14 days. Side effects: gallstones, sinus bradycardia.
Dopamine agonists	Bromocriptine, cabergoline: Used if prolactin secretion is present. Cabergoline is more effective.
GH receptor antagonist	Pegvisomant: Used for somatostatin non-responders. Normalizes IGF-1 in 90% of patients. Requires liver function monitoring.
Radiotherapy	Stereotactic radiotherapy preferred. Side effect: Hypopituitarism (annual hormone testing required).

Prognosis

- **Left ventricular failure** is the most common cause of death if untreated.

> **Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients**

Pituitary adenoma

Epidemiology

- Small pituitary tumours (<4 mm) are common, found in **10%** of MRIs, though few cause symptoms.

Classification

By Size	By Hormone Secretion
Microadenoma: ≤ 10 mm	**Secretory Adenomas** (60%): Hyperpituitarism
Macroadenoma: > 10 mm	- **Prolactinoma**: 35–40% (most common) - **Somatotroph adenoma** (GH): 10–15% (acromegaly) - **Corticotroph adenoma** (ACTH): 5–10% (Cushing's disease) - **Thyrotroph adenoma** (TSH): <5%
	Non-secretory Adenomas (30–35%): Asymptomatic or hypopituitarism with mass effects

Clinical Features

Adenoma Type	Manifestation
Secretory Microadenomas	Hyperpituitarism (e.g., acromegaly, prolactinoma).
Secretory Macroadenomas	Hyperpituitarism + Mass effects (e.g., headaches, bitemporal hemianopsia, diplopia).
Non-secretory Microadenomas	Usually asymptomatic.
Non-secretory Macroadenomas	Hypopituitarism + Mass effects.
Mass Effects	Superior extension → Optic chiasm compression Lateral extension → Cranial nerve involvement (III, IV, VI) causing diplopia.

Diagnostics

- **Hormone Assays**: Basal prolactin, IGF-1, 24-hour urine cortisol, thyroid function tests.
- **MRI with contrast**: Reveals an intrasellar mass.
- **Perimetry**: To assess visual field defects.

Management

Type	Treatment
Non-secretory Microadenomas	No treatment needed; follow-up with serial MRI.
Prolactinomas	- **First-line**: Dopamine agonists (e.g., cabergoline, bromocriptine). - **Second-line**: Trans-sphenoidal hypophysectomy ± radiotherapy.
Other Secretory Adenomas	- **First-line**: Transsphenoidal hypophysectomy. - **Second-line**: Medications ± irradiation.
Macroadenomas with Mass Effects	Surgery to prevent optic chiasm compression (especially for tumours >1.5 cm).

Pituitary Apoplexy

- **Definition**: Sudden haemorrhage into the pituitary gland, often in patients with existing adenomas.
- **Features**: Retro-orbital headache, visual disturbances, ACTH deficiency (Addisonian crisis), nausea, hypotension.
- **Diagnosis**: MRI.
- **Treatment**:
  - **Acute**: Urgent corticosteroid replacement (e.g., hydrocortisone).
  - **Surgery**: Indicated if severe neuro-ophthalmic signs (e.g., deteriorating visual field defects).
  - **Long-term**: Hormone replacement therapy (e.g., corticosteroids, testosterone, thyroid hormone).

Hyperprolactinaemia

Definition

- **Hyperprolactinaemia** refers to an elevated level of prolactin in the blood.

Epidemiology

- **Most common form of hyperpituitarism.**
- More common in females.
- **Microprolactinomas** are more prevalent than macroprolactinomas.
- **10% of the population** may have pituitary microadenomas without symptoms.

Causes

Causes of raised prolactin – the **P**s
* **P**regnancy
* **P**rolactinoma
* **P**hysiological
* **P**olycystic ovarian syndrome
* **P**rimary hypothyroidism
* **P**henothiazines, metoclopramide, domperidone

Clinical Features

Gender	Symptoms
Men	Impotence, erectile dysfunction, loss of libido, galactorrhoea (rare).
Women	Amenorrhoea, galactorrhoea, reduced libido.
Mass Effects	Headaches, visual defects, cranial nerve palsies (in macroadenomas).
Long-term Risks	Reduced bone mineral density (BMD).

Diagnostic Tests

- **Serum Prolactin Levels:**
  - <1000 mU/L: Likely drug-induced.
  - 1000–3000 mU/L: Microprolactinoma.
    - 3000 mU/L: Macroprolactinoma.
  - **Hook Effect:** Falsely low PRL levels in large tumours due to assay interference; corrected by sample dilution.
- **Other Tests:**
  - Thyroid and renal function tests.
  - MRI of the brain to detect adenomas or tumours.

Treatment

Type	Details
Dopamine Agonists	- **Cabergoline**: More effective, longer-acting, and better-tolerated. - **Bromocriptine**: Preferred during pregnancy.
Surgery	Rarely required; reserved for resistant or intolerant cases.
Radiotherapy	Used in refractory cases to reduce recurrence risk.

Management During Pregnancy

- **Pre-pregnancy:** Dopamine agonists to reduce adenoma size; surgery if large tumours persist.
- **During Pregnancy:** Discontinue dopamine agonists unless symptoms arise.
- **Monitoring:** MRI (without gadolinium) if visual disturbances occur.
- **Breastfeeding:** Avoid dopamine agonists unless symptoms necessitate treatment.

Cabergoline VS Bromocriptine

Comparison	Cabergoline	Bromocriptine
Dopamine receptors	D2 selectively	D2 and other dopamine receptors
Half-life	long acting (once or twice weekly → better tolerability and patient compliance)	Short acting (requires multiple doses per day)
Effectiveness in lowering the prolactin	More effective in lowering the prolactin	Less effective
Safety during pregnancy	Less data about safety	Less teratogenicity than cabergoline

Thyroid disorders

Hypothyroidism

Epidemiology

- Affects **1-2% of women** in the UK.
- **5-10 times more common** in females than males.

Causes of Hypothyroidism

Cause	Details
Hashimoto's Thyroiditis	Autoimmune disease, most common cause. Associated with other autoimmune disorders and syndromes (e.g., Down's syndrome, coeliac disease).
Dietary Iodine Deficiency	Common in parts of central Africa. Iodine requirement: 150 mcg/day (adults), 200 mcg/day (pregnant women).
Postpartum Thyroiditis	Subacute lymphocytic thyroiditis.
De Quervain's Thyroiditis	Subacute granulomatous thyroiditis.
Riedel Thyroiditis	Dense fibrosis replacing normal thyroid tissue.
Iatrogenic Causes	After thyroidectomy, radioiodine therapy, or use of anti-thyroid drugs.
Drug-Induced	Amiodarone, lithium (causes goitre and hypothyroidism).
Central Hypothyroidism	Pituitary disorders → ↓TSH → ↓ T4.
Tertiary Hypothyroidism	Hypothalamic disorders → ↓ TRH → ↓ TSH → ↓ T4.

Clinical Features

Category	Symptoms
Decreased Metabolic Rate	Fatigue, cold intolerance, weight gain, dry skin, brittle nails, Woltman sign (delayed reflex relaxation).
Sympathetic Depression	Cold skin, decreased sweating, constipation, bradycardia.
Myxedema Features	Puffy appearance, hoarse voice, pretibial and periorbital oedema, cardiomyopathy, dyspnea.
Hyperprolactinaemia Symptoms	Amenorrhoea, galactorrhoea, erectile dysfunction, decreased libido.
Cognitive Symptoms	Impaired cognition, depression, somnolence.

Investigations

- **Thyroid Function Tests:** TSH (best screening test) and FT4.
- **Anti-TPO Antibodies:** Present in **10%** of women without thyroid pathology.
- **Associated Lab Findings:**
  - Euvolaemic hyponatraemia, elevated creatine kinase (hypothyroid myopathy).
  - Mixed dyslipidaemia (↑LDL, ↑triglycerides), glucose intolerance.
  - Hyperprolactinaemia from increased TRH secretion.

- Pericardial or pleural effusions (clinically silent).
- **TSH Monitoring:** Persistent elevation despite treatment may indicate non-compliance, drug interactions, or malabsorption syndromes.

Management

- **Levothyroxine (T4) Replacement:**
  - **Dose:**
    - 25 mcg/day for patients with cardiac disease or >50 years.
    - 50–100 mcg/day for others.
  - **Target TSH:** 0.5–2.5 mU/L.
  - **Follow-up:** Reassess TSH every **8-12 weeks** after dosage changes.
- **Myxedema Coma (Emergency):**
  - Treat with **IV levothyroxine + liothyronine**, hydrocortisone, and rewarming.

Monitoring & Complications

- **TSH Monitoring Indicators:**
  - ↑ **TSH** with normal FT4 → Poor compliance.
  - ↓ **TSH** with elevated FT4 → Over-replacement.
- **Complications:**
  - **Myxedema Coma:** Life-threatening, often in elderly non-compliant patients.
  - **Hashimoto's Encephalopathy:** Rare autoimmune encephalopathy; steroid-responsive.
  - **Primary Thyroid Lymphoma:** Linked to long-standing Hashimoto's thyroiditis.
  - **Statin-Induced Myopathy:** More likely in hypothyroid patients; correct thyroid status before increasing statin dose.

Riedel's thyroiditis

Category	Details
Definition	A rare form of chronic thyroiditis characterized by **dense fibrosis** that replaces normal thyroid tissue.
Epidemiology	Extremely rare; often seen in middle-aged adults. Higher prevalence in women.
Pathophysiology	- Progressive fibrotic process that extends beyond the thyroid into surrounding neck structures. - May be linked to IgG4-related systemic diseases.
Clinical Features	- **Painless goitre**: Hard, non-tender thyroid. - Compressive symptoms: Dysphagia, hoarseness, dyspnoea (due to tracheal compression). - Hypothyroidism due to gland destruction.
Differential Diagnosis	Other forms of thyroiditis (e.g., Hashimoto's, De Quervain's), malignancies, or fibrosing disorders.
Investigations	- **Thyroid function tests:** May show hypothyroidism. - **Imaging:** Ultrasound or CT to assess fibrosis. - **Biopsy:** Confirms diagnosis by showing dense fibrotic tissue without malignancy.

Category	Details
Complications	- Tracheal or oesophageal compression. - Hypothyroidism. - Association with other fibrotic conditions (e.g., retroperitoneal fibrosis).
Treatment	- **Corticosteroids:** To reduce inflammation. - **Surgery:** For severe compressive symptoms (e.g., tracheal stenosis). - **Thyroid hormone replacement** for hypothyroidism.

Sick Euthyroid Syndrome (Non-Thyroidal Illness Syndrome)

Category	Details
Definition	A state in which thyroid function tests are abnormal despite normal thyroid gland function. Often occurs in critically ill or hospitalized patients without primary thyroid disease.
Epidemiology	Common in patients with severe illness (e.g., sepsis, cardiac disease, trauma, burns) and during fasting or malnutrition.
Pathophysiology	- Decreased conversion of **T4 to T3** due to reduced deiodinase activity. - Increased reverse T3 (rT3), an inactive form of T3, due to reduced clearance. - Cytokines and inflammatory markers (e.g., IL-6, TNF-alpha) affect hypothalamic-pituitary-thyroid axis regulation.
Thyroid Function Tests	- **Low T3 levels** (most common finding). - **Normal or low T4 levels.** - **Normal or slightly decreased TSH.** - Elevated **reverse T3** (rT3).
Clinical Features	No specific symptoms of thyroid disease; symptoms reflect the underlying critical illness.
Differential Diagnosis	Hypothyroidism (distinguishing from primary thyroid disease is essential).
Management	- Treatment focuses on the **underlying illness** rather than thyroid hormone replacement. - Thyroid hormone therapy (e.g., T3) may be considered in rare cases with severe low T3 syndrome.
Prognosis	- **Usually resolves** with recovery from the underlying illness. - Persistently abnormal thyroid tests may indicate poor prognosis or unresolved illness.

Subclinical hypothyroidism

Diagnosis: Elevated TSH with normal T4 and T3.

Epidemiology

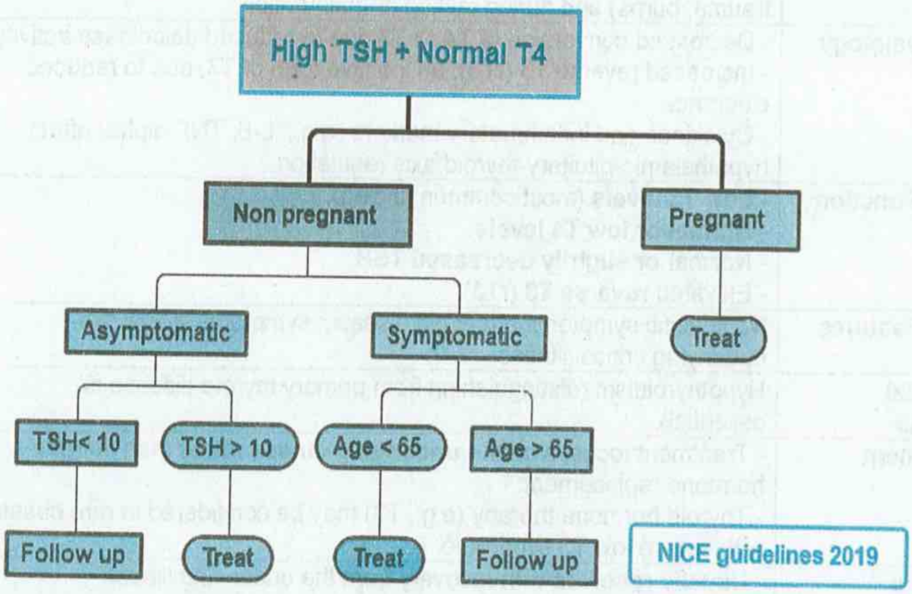
- found in 8–10% of the population. More common in young women and increases with age.

Significance

- may be associated with an increased risk of cardiovascular disease
- **Adverse pregnancy outcome**: ↑risk of severe preeclampsia, placental abruption, preterm birth
  - ⇨ subclinical hypothyroidism with positive anti-thyroid peroxidase (TPO) antibodies tend to have the highest risk of adverse pregnancy outcomes

Indications for treatment

- **TSH > 10**
- Hypothyroid symptoms (regardless TSH level)
- Pregnancy or pregnancy planned in the near future



Management

TSH Levels	Management Strategy
TSH 4-10 mU/L	**Symptomatic Patients:** - **<65 years:** 6-month trial of levothyroxine; stop if no improvement. - **>80 years:** 'Watch and wait' strategy, generally avoiding hormonal treatment. **Asymptomatic Patients:** Monitor thyroid function and recheck after 6 months.
TSH >10 mU/L	- Start **levothyroxine treatment**, even if asymptomatic, to prevent progression to overt hypothyroidism.

Monitoring

Scenario	Monitoring Frequency
Untreated subclinical hypothyroidism	- With previous thyroid disease (e.g., surgery, antibodies): Once per year. - Without thyroid disease features: Once every 2-3 years.
After Stopping Treatment	Same frequency as above, based on thyroid disease history.

Post-partum thyroiditis

Category	Details
Definition	Thyroid dysfunction occurring within the **first 6 months** after delivery.
Course of Disease	Typically presents with **hyperthyroidism** followed by **hypothyroidism**, with recovery in one-third of cases. Other patients may show a single-phase pattern or reversed phases.
Features	The characteristic sequence: **Hyperthyroid phase → Hypothyroid phase → Recovery phase.**
Pathophysiology	Likely autoimmune; **lymphocytic infiltration** of the thyroid is typical.
Prevalence	Occurs in **5-7%** of women post-partum.
Risk Factors	- Presence of **TPO antibodies** before delivery. - Twice as common in patients with **type 1 diabetes mellitus**.
Investigations	**TPO antibodies** are positive in **90%** of cases.

Management

Phase	Treatment
Thyrotoxic Phase	- Usually no anti-thyroid drugs as the thyroid is not overactive. - **Beta-blockers** (e.g., propranolol) for symptomatic relief (e.g., tremor, anxiety).
Hypothyroid Phase	- **Thyroxine** replacement therapy if needed. - Thyroxine is stopped after **6 months** to reassess thyroid function, with re-evaluation in 1 month.

Prognosis

- **Recurrence** is common in subsequent pregnancies.
- **Permanent hypothyroidism** develops in **up to 40%** of patients.

Subacute (De Quervain's) thyroiditis

Category	Details
Definition	Also known as **De Quervain's thyroiditis** or **subacute granulomatous thyroiditis**.
Pathophysiology	Follows a **viral infection**. Thyroid inflammation leads to the release of stored thyroid hormone, rather than increased production of T3/T4. Associated with **HLA-B35**.
Features	- **Tender goitre** (painful, rapid thyroid enlargement). - **Triphasic course**: Hyperthyroidism → Hypothyroidism → Euthyroidism. - Flu-like symptoms with fever.
Investigations	- **Hyperthyroidism** during the early phase, followed by hypothyroidism. - **Raised ESR** (>50-100) and elevated CRP. - **Thyroid ultrasound:** Hypoechoic areas with decreased vascular flow. - **Thyroid scintigraphy:** Globally reduced uptake (<1%) on iodine-131 scan.
Management	- **Self-limiting** in most cases; no specific treatment required. - **Beta-blockers** for hyperthyroid symptoms. - **Aspirin or NSAIDs** for thyroid pain relief. - **Steroids (prednisolone)**: For severe cases or persistent hypothyroidism.
Prognosis	- **Return to normal thyroid function** in >90% of cases. - **5% of patients** may develop long-term hypothyroidism requiring thyroid hormone replacement. - Recurrences are uncommon.

In De Quervain's thyroiditis, treatment is aimed at reducing inflammation with NSAIDS or steroids in severe cases (e.g. prednisolone 20–40 mg/day for two weeks and titrated down).

Thyrotoxicosis with tender goitre = Subacute thyroiditis (De Quervain's thyroiditis)

Subclinical hyperthyroidism

Category	Details
Definition	Normal **free T4 and T3 levels** with **low TSH** (<0.1 mU/L).
Causes	- **Graves' disease** or autonomously functioning thyroid nodules suppressing TSH secretion. - **Multinodular goitre** (especially in elderly women). - **Excessive thyroxine** use.
Complications	- **Cardiovascular:** Atrial fibrillation. - **Bone metabolism:** Increased risk of osteoporosis. - **Cognitive impact:** Increased likelihood of dementia. - Reduced quality of life.

Category	Details
Management	- **Observation:** Repeat TSH, FT4, and FT3 measurements. Levels may normalize without treatment. - **Trial of low-dose antithyroid drugs:** For 6 months to induce remission if needed. - **Definitive Therapy Indications:** Persistent low TSH (<0.1 mU/L) and: - Symptoms of hyperthyroidism, osteoporosis (assessed by DEXA scan), atrial fibrillation, or unexplained weight loss.
Guidelines	- **American Association of Clinical Endocrinologists:** Recommends treatment for: - Patients over 65 years. - Those at risk for **osteoporosis** or **heart disease**.

Thyrotoxicosis

Causes

- **Autoimmune and Nodular Causes:**
  - **Graves' disease** (50-60% of cases)
  - **Toxic nodular goitre** (Multinodular goitre, TNG)
  - **Toxic adenoma** (Plummer's disease)
- **Thyroiditis:**
  - **Subacute granulomatous thyroiditis** (De Quervain's thyroiditis)
  - **Subacute lymphocytic thyroiditis** (Postpartum thyroiditis)
  - **Hashitoxicosis:** Transient thyrotoxicosis in early Hashimoto's thyroiditis.
- **Drug-induced:** Amiodarone, excess iodine (Jod-Basedow phenomenon).
- **Secondary Thyrotoxicosis:**
  - **TSH-producing pituitary adenoma**
  - **Ectopic TSH production** (e.g., struma ovarii, ovarian teratomas).
- **Factitious Thyrotoxicosis:** Exogenous thyroid hormone abuse.

Clinical Features

- **General:** Heat intolerance, weight loss, excessive sweating, frequent bowel movements, fatigue, tremors, onycholysis, pretibial myxedema.
- **Goitre:** Diffuse, smooth goitre with possible bruit.
- **Eyes:** Lid lag, lid retraction, exophthalmos (Graves' ophthalmopathy).
- **Cardiovascular:** Tachycardia, atrial fibrillation, hypertension with widened pulse pressure.
- **Musculoskeletal:** Hyperthyroid myopathy, osteoporosis, fine tremors.
- **Endocrinological:** Menstrual irregularities, gynecomastia, infertility.

Investigations

- **Thyroid Function Tests:** Low TSH with elevated T4/T3 (T3 thyrotoxicosis possible).
- **TSH Receptor Antibodies (TRAb):** For Graves' disease diagnosis.
- **Thyroid Ultrasound:** Assess goitre, nodules, and vascularity.
- **Thyroid Scintigraphy:** Radioactive iodine uptake to differentiate causes.
  - **Increased uptake:** Graves' disease, toxic adenoma, toxic nodular goitre.
  - **Decreased uptake:** Thyroiditis, exogenous hormone use.

Management

- **Symptom Control:** Beta-blockers (e.g., propranolol) for hyperadrenergic symptoms.
- **Antithyroid Drugs (ATDs):**
  - **Methimazole:** First-line for most cases.
  - **Propylthiouracil (PTU):** For thyroid storm or early pregnancy.
- **Radioactive Iodine Therapy (RAI):**
  - Used for toxic goitres and refractory Graves' disease.
  - Contraindicated in pregnancy and breastfeeding.
- **Surgery:** Reserved for large goitres, obstructive symptoms, or malignancy.

Complications

- **Cardiovascular:** Atrial fibrillation, heart failure.
- **Skeletal:** Osteoporosis due to T3-mediated bone resorption.
- **Ophthalmopathy:** Worsened in Graves' disease after RAI.

Management in Pregnancy

- **First Trimester:** PTU is preferred.
- **Second and Third Trimester:** Switch to carbimazole due to PTU hepatotoxicity risks.
- **Postpartum:** Carbimazole preferred during breastfeeding.

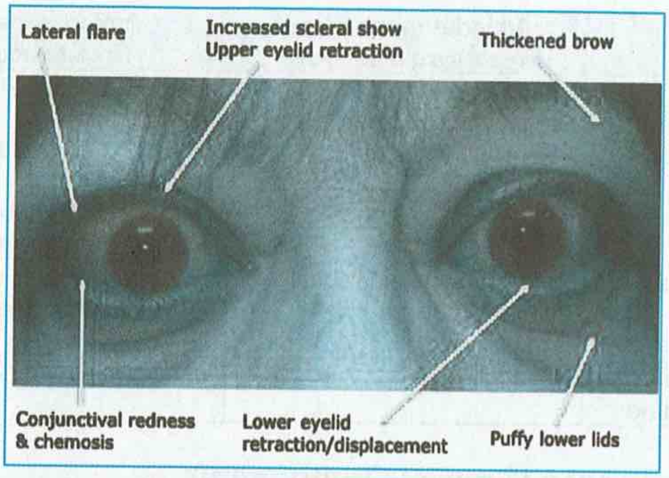
Amiodarone-induced thyroid dysfunction

Feature	Amiodarone-Induced Hypothyroidism (AIH)	Amiodarone-Induced Thyrotoxicosis (AIT)
Prevalence	More common in iodine-sufficient areas	More common in iodine-deficient areas
Pathophysiology	Excess iodine inhibits thyroid hormone synthesis (Wolff-Chaikoff effect)	Due to excess iodine (Type 1) or thyroid inflammation/destruction (Type 2)
Types	Single type	- **Type 1**: Iodine-induced in patients with underlying thyroid disease - **Type 2**: Destructive thyroiditis without pre-existing thyroid disease
Risk Factors	Pre-existing autoimmune thyroid disease	Type 1: Pre-existing thyroid disease (e.g., multinodular goiter) Type 2: No pre-existing thyroid disease
Thyroid Function Tests	- **TSH**: Elevated - **Free T4 and T3**: Low	- **TSH**: Suppressed - **Free T4 and T3**: Elevated
Thyroid Antibodies	May be positive in autoimmune thyroid disease	- Type 1: May be positive - Type 2: Usually negative
Thyroid Ultrasound	Normal or mildly enlarged	- Type 1: Increased vascularity - Type 2: Hypoechoic areas, reduced vascularity

Feature	Amiodarone-Induced Hypothyroidism (AIH)	Amiodarone-Induced Thyrotoxicosis (AIT)
Treatment	- **Levothyroxine** for symptomatic patients - Continue amiodarone if necessary	- **Type 1**: Antithyroid drugs (e.g., methimazole) - **Type 2**: Glucocorticoids (e.g., prednisone) - Mixed type: Combination of antithyroid drugs and glucocorticoids
Refractory Cases	Rarely requires additional treatment beyond levothyroxine	**Thyroidectomy** in severe, unresponsive cases with cardiac risk
Effectiveness of Radioactive Iodine	Not applicable	Ineffective due to high iodine load

Thyroid eye disease (Graves' Orbitopathy)

Category	Details
Definition	Autoimmune disease affecting the orbit and retro-ocular tissues, commonly seen in **Graves' disease (25%)** and rarely in **Hashimoto's thyroiditis**.
Risk Factors	Genetics, high TSH receptor antibodies (TSHRAb), female sex, smoking, prior radioiodine therapy, high serum cholesterol.
Features	- Mostly occurs in **hyperthyroidism**, but also seen in **euthyroid (5%)** and **hypothyroid (5%)** states. - **Bilateral** presentation common, but can be **unilateral (15%)**. - **Lid retraction:** Visible sclera below/above eyelids. - **Lid lag:** Sclera visible above iris during downgaze. - **Exophthalmos (proptosis):** Eye(s) protrude out of the orbit, potentially compressing the optic nerve and reducing vision.
Pathophysiology	- TSH receptor antibodies (TSHRAb) trigger excessive fibroblast proliferation → Retro-orbital tissue expansion. - Hyperthyroidism activates beta receptors of cranial nerve III, stimulating levator palpebrae superioris muscle → Lid retraction and lid lag.
Prevention	- **Avoid smoking** and **radioiodine therapy**. - Administer **steroids** 1-2 weeks before starting radioiodine therapy.
Investigations	- **Thyroid function tests:** ↓ TSH, ↑ Free T3/T4, ↑ TSHRAb. - **CT/MRI (non-contrast)** of the orbits: Preferred imaging modality.
Management	- **Eye protection:** Artificial tears, lubricants, and raising the head of the bed. - **Mild cases:** Local eye care measures. - **Moderate-to-severe cases:** Glucocorticoids (initial therapy). - **Sight-threatening cases:** IV glucocorticoids (e.g., methylprednisolone 0.5–1 g daily for 3 days) and hospitalization for potential **urgent orbital decompression surgery**. - **Avoid smoking** and treat **underlying hyperthyroidism**.



Thyroid storm (crisis)

Definition: acute exacerbation of thyrotoxicosis.

Precipitating factors

- Any acute stressful condition such as surgery or trauma
- Acute infections
- Acute iodine load e.g. CT contrast media
- Postpartum
- When antithyroid drugs are being withdrawn.

Features

- Altered mental status (confusion, agitation, delirium, somnolence, convulsion, and coma)
- Fever > 38.5C
- Tachycardia
- Nausea, vomiting, and diarrhea
- Jaundice
- Hypertension
- Multisystem decompensation: heart failure, respiratory distress, prerenal failure, abnormal liver function test.

Diagnosis

- Low/undetectable TSH, elevated free T3/T4 (but may not be grossly elevated)

Management

Category	Details
Admission	**Intensive Care Unit (ICU)** admission for close monitoring and supportive care.
Symptomatic Treatment	- **Tachycardia:** Propranolol 60–80 mg every 4–6 hours. - **Hypotension/ Hypovolemia:** Fluid resuscitation. - **Hyperpyrexia:** Paracetamol; chlorpromazine (50–100 mg IM) can also control agitation and hyperpyrexia by affecting central thermoregulation.
Antithyroid Drugs	- **Thyroid Hormone Synthesis Inhibition:** Propylthiouracil (PTU) 600 mg–1 g loading dose, followed by 200–300 mg every 4 hours via NG tube or rectally.
Thyroid Hormone Release Inhibition	- **Potassium Iodide Solution (SSKI):** 5 drops (50 mg iodide/drop) every 6 hours, started at least 1 hour after antithyroid drugs. - **Lugol's Solution:** 10 drops (6.25 mg iodide/iodine per drop) orally three times daily.
Peripheral T4 to T3 Conversion Inhibition	**Glucocorticoids:** Hydrocortisone 300 mg loading dose, followed by 100 mg every 8 hours.
Enterohepatic Circulation Inhibition	**Bile acid sequestrants:** Cholestyramine 4 grams, four times daily, for severe cases.
Rescue Therapy	**Plasmapheresis or peritoneal dialysis** may be used for refractory cases.

Treatment of thyroid storm → 5 'Bs':

1. **B**lock synthesis (i.e. antithyroid drugs)
2. **B**lock release (i.e. iodine)
3. **B**lock T4 into T3 conversion (i.e. high-dose propylthiouracil, propranolol, corticosteroid)
4. **B**eta-blocker
5. **B**lock enterohepatic circulation (i.e. cholestyramine).

Thyroid cancer

Category	Details
Epidemiology	- Accounts for <1% of all cancers. - More common in **females aged 30–50 years.**
Risk Factors & Associations	- **External irradiation:** Associated with papillary carcinoma. - **Genetic mutations:** - BRAF (Papillary) - RET (Medullary, MEN2) - RAS (Follicular) - TP53 (Anaplastic) - **Autoimmune thyroiditis:** Linked with thyroid lymphoma.
Types and Characteristics	**Papillary (80%):** Young females, local spread, excellent prognosis. **Follicular (10%):** Hematogenous spread, good prognosis. **Medullary (5%):** Part of MEN2, poor prognosis, secretes calcitonin. **Lymphoma (2%):** Associated with Hashimoto's, poor prognosis. **Anaplastic (1–2%):** Aggressive, very poor prognosis.

Category	Details
Medullary Thyroid Carcinoma	- Derived from **C cells** (neural crest). - Secretes **calcitonin** → flushing, diarrhea. - **Screening:** Pentagastrin stimulation test (rise in calcitonin). - Investigate for MEN2 (calcium, metanephrines, RET mutation).
Investigations	- **Thyroid Ultrasound:** Hypoechoic nodules, irregular margins, microcalcifications. - **Fine-Needle Aspiration (FNA):** Confirms diagnosis. - **Thyroid Scintigraphy:** Identifies non-functioning (cold) nodules. - **Tumor Markers:** Thyroglobulin (papillary/follicular), Calcitonin (medullary).
Management	- **Surgery:** Total thyroidectomy ± neck dissection for nodal spread. - **Hemithyroidectomy:** For small (<2 cm) low-risk tumors. - **Radioactive Iodine Ablation (RAIA):** For well-differentiated cancers. - **Chemotherapy/Radiation:** For poorly differentiated cancers.
Post-Operative Care	- **Thyroxine Replacement:** Suppress TSH (high-risk: <0.1 mU/L, low-risk: 0.5–2.0 mU/L). - **Monitoring:** Annual TSH, thyroglobulin, ultrasound for recurrence.
Recurrent Disease	- **Thyroglobulin (Tg) Monitoring:** Detects recurrence. - **RAI Uptake Scan:** Identifies metastases. - **Treatment:** Surgery for local recurrence, radioactive iodine for uptake-positive tumors.

Thyroid ultrasound

- **Ultrasonographic criteria associated with higher risk of malignancy:**
  1) Low echodensity (Hypoechogenicity)
  2) **Microcalcifications: the most predictive feature of malignancy**
  3) Irregular borders (poorly-defined margin)
  4) Increased intranodular vascularity: (↑↑marginal blood flow → benign adenoma, ↑↑ intranodular blood flow → thyroid cancer)
  5) Absence of a halo
  6) Taller-than-wide configuration on transverse view
- **Ultrasound "U" classification of thyroid nodules**

Classification	Criteria
U1 (normal)	- no nodules
U2 (benign)	- hyperechoic or isoechoic with a halo - cystic change with ring down artifact (colloid) - microcystic or spongiform appearance - peripheral egg-shell calcification - peripheral vascularity

Classification	Criteria
U3 (indeterminate)	- solid homogenous markedly hyperechoic nodule with halo (follicular lesions) - hypoechoic with equivocal echogenic foci or cystic change - mixed or central vascularity
U4 (suspicious)	- solid hypoechoic (compared with thyroid) - solid very hypoechoic (compared with strap muscles) - hypoechoic with disrupted peripheral calcification - lobulated outline
U5 (malignant)	- solid hypoechoic with a lobulated or irregular outline and microcalcification (papillary carcinoma) - solid hypoechoic with a lobulated or irregular outline and globular calcification (medullary carcinoma) - intranodular vascularity - taller than wide axially (AP>ML) - characteristic associated lymphadenopathy

- **The need for Fine Needle Aspiration Cytology (FNAC) according to US:**

U1-2	**not requiring FNAC, unless the patient has a statistically high risk of malignancy**
U 3 - 5	FNAC should be done

Fine needle aspiration (FNA)

- the gold standard diagnostic tool for thyroid nodules. but follicular neoplasia can only be diagnosed histologically.
- **Diagnostic categories from FNAC (The royal college of pathologist classification)**

	Category	Action
Thy 1	Non-diagnostic. Inadequate	Repeat sampling, using US if necessary
Thy 2	Non-neoplastic	Two samples, 3–6 months apart, showing benign appearances are indicated to exclude neoplasia. If rapid growth/pressure effects/high risk, diagnostic lobectomy may be indicated
Thy 3 (Thy3f)	(i) Follicular lesions	Lobectomy (diagnostic hemithyroidectomy) (because follicular adenoma or follicular carcinoma cannot be distinguished on cytology alone) with completion thyroidectomy if malignant (up to 20% risk of malignancy)
Thy 3 (Thy3a)	(ii) atypical features, other suspicious findings	Many Thy3a cases reflect suboptimal specimens → Discussion at thyroid cancer MDT → Repeat FNAC
Thy 4	Suspicious of malignancy	Surgical excision for differentiated tumour (80% risk of malignancy) (diagnostic hemithyroidectomy)
Thy 5	Diagnosis of malignancy	Surgical excision for differentiated thyroid cancer (>95% risk of malignancy). Radiotherapy/ chemotherapy for anaplastic thyroid cancer, lymphoma/metastases

Parathyroid and Bone disorders

Hypercalcaemia

Definition

- Elevated serum calcium levels, typically >2.6 mmol/L (10.5 mg/dL).

Causes

1. **Primary Hyperparathyroidism**:
   - Most common cause in outpatients.
   - Excess PTH production increases calcium levels.
2. **Malignancy**:
   - **Humoral hypercalcemia of malignancy**: Tumors secrete parathyroid hormone-related peptide (PTHrP).
   - **Local osteolytic hypercalcemia**: Bone metastases (e.g., breast, lung cancers).
3. **Vitamin D Excess**:
   - Excessive supplementation or granulomatous diseases (e.g., sarcoidosis, tuberculosis) that produce active vitamin D.
4. **Medications**:
   - Thiazide diuretics (reduce renal calcium excretion), lithium, vitamin A toxicity.
5. **Endocrine Disorders**:
   - Hyperthyroidism, adrenal insufficiency, and pheochromocytoma.
6. **Genetic Disorders**:
   - Familial hypocalciuric hypercalcemia (FHH).

Pathophysiology

- Hypercalcemia increases **threshold for neuron excitability**, resulting in reduced neuromuscular activity. It also affects **renal concentrating ability** and **GI motility**.

Clinical Features

- **Neuromuscular**: Fatigue, muscle weakness, confusion, and lethargy.
- **Renal**: Polyuria, polydipsia, nephrolithiasis, and nephrocalcinosis.
- **Gastrointestinal**: Nausea, constipation, abdominal pain.
- **Cardiovascular**: Shortened QT interval, arrhythmias, and hypertension.

Diagnosis

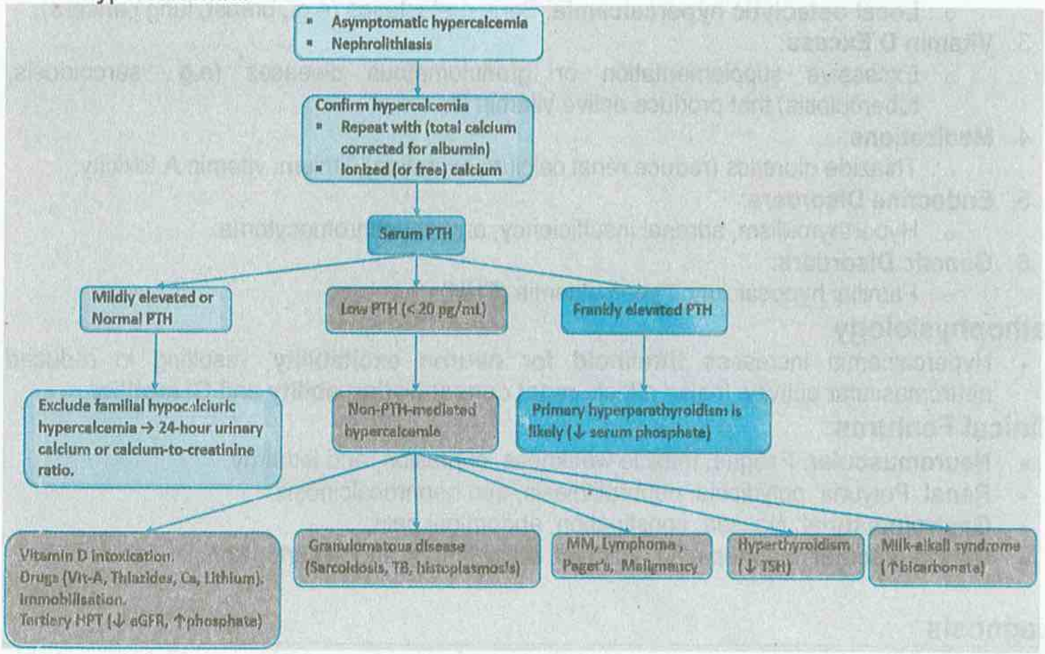
Parameter	Findings in Hypercalcemia
Serum Calcium	Elevated (>2.6 mmol/L)
PTH	High in primary hyperparathyroidism, low in malignancy
PTHrP	Elevated in humoral hypercalcemia of malignancy
Vitamin D	Elevated in vitamin D toxicity
Urinary Calcium	Differentiates primary hyperparathyroidism (high) from FHH (low)

Management

1. **IV Fluids**:
   - Normal saline to correct dehydration and promote renal calcium excretion.
2. **Diuretics**:
   - Loop diuretics (e.g., furosemide) after hydration to enhance calcium excretion.
3. **Bisphosphonates**:
   - Zoledronic acid or pamidronate for malignancy-related hypercalcemia.
4. **Calcitonin**:
   - Short-term use to lower calcium rapidly in severe cases.
5. **Glucocorticoids**:
   - For vitamin D toxicity and granulomatous diseases (e.g., sarcoidosis).
6. **Dialysis**:
   - In severe or refractory cases, particularly in patients with renal failure.

Key Points for MRCP Candidates

1. Primary hyperparathyroidism and malignancy are the most common causes.
2. **PTH levels** help differentiate between hyperparathyroidism (high PTH) and malignancy (low PTH).
3. **Hydration and bisphosphonates** are mainstays of treatment for symptomatic hypercalcemia.



Familial hypocalciuric hypercalcaemia (FHH)

Definition

- A rare, benign genetic disorder characterized by **mildly elevated serum calcium** levels and **low urinary calcium excretion**.

Pathophysiology

- Caused by mutations in the **calcium-sensing receptor (CaSR) gene**.
- Leads to **reduced sensitivity** of the parathyroid glands and kidneys to calcium, resulting in **higher serum calcium set-points** and reduced calcium excretion.

Genetics

- **Autosomal dominant inheritance**.
- **CaSR gene mutations** on chromosome 3.

Clinical Features

- Usually **asymptomatic**, often discovered incidentally.
- Mild hypercalcemia without typical symptoms of hypercalcemia (e.g., no significant bone, kidney, or gastrointestinal symptoms).
- **PTH levels are normal or slightly elevated.**

Diagnosis

Parameter	Findings in FHH
Serum Calcium	Mildly elevated
Urinary Calcium	Low (<100 mg/24 hours or <0.01 mmol/L)
PTH	Normal or mildly elevated

- **Urine calcium to creatinine clearance ratio**: Typically <0.01, distinguishing FHH from primary hyperparathyroidism.

Differential Diagnosis

- **Primary Hyperparathyroidism**: Differentiated by higher urinary calcium levels in primary hyperparathyroidism.

Management

- Generally **no treatment required** due to the benign nature.
- Avoid unnecessary parathyroidectomy, as surgery does not correct hypercalcemia in FHH.

Key Points for MRCP Candidates

1. **Mild hypercalcemia** with **low urinary calcium** is the hallmark.
2. **Genetic testing** for CaSR mutation confirms diagnosis.
3. **No treatment needed**, and parathyroid surgery is ineffective.

Hypocalcaemia

Category	Details
Definition	Serum calcium level typically below **2.2 mmol/L (8.5 mg/dL)**. Ionized calcium <1.1 mmol/L is also indicative of hypocalcemia.
Causes	- **Vitamin D Deficiency**: Insufficient sunlight exposure, dietary deficiency, malabsorption disorders (e.g., celiac disease, Crohn's disease) - **Hypoparathyroidism**: Surgical removal or damage to parathyroid glands, autoimmune destruction - **Chronic Kidney Disease (CKD)**: Decreased activation of vitamin D - **Hypomagnesemia**: Reduces PTH release and activity - **Medications**: Bisphosphonates, calcitonin, certain anticonvulsants
Pathophysiology	Calcium is essential for muscle contraction, nerve transmission, and blood clotting. Low calcium impairs these processes, leading to increased neuromuscular excitability and tetany.
Clinical Features	- **Neuromuscular**: Muscle cramps, spasms, tingling in extremities, facial twitching (Chvostek sign), carpopedal spasm (Trousseau sign), tetany, seizures - **Cardiovascular**: Prolonged QT interval on ECG, hypotension - **Chronic Hypocalcemia**: Brittle nails, dry skin, hair loss, cataracts
Diagnosis	- **Serum Calcium**: Total and ionized levels - **Associated Tests**: Serum magnesium, phosphate, PTH, and vitamin D levels to identify underlying cause.
Management	- **Acute Hypocalcemia**: - **IV Calcium Gluconate**: 10-20 mL of 10% solution over 10-20 minutes, repeat as needed for severe symptoms. - **Chronic Hypocalcemia**: - **Oral Calcium Supplements**: 1-2 grams daily of elemental calcium. - **Vitamin D Supplementation**: 800-1,000 IU daily, higher doses if malabsorption or CKD is present. - **Correct Hypomagnesemia**: Often required as low magnesium impairs calcium regulation.
Key Points for MRCP	1. **Chvostek and Trousseau signs** are classic neuromuscular findings. 2. **IV calcium gluconate** is used in emergencies, while oral calcium and vitamin D are for maintenance. 3. **Check magnesium levels**, as hypomagnesemia can worsen or cause hypocalcemia.

Magnesium deficiency causes hypocalcaemia

Hypomagnesaemia

Category	Details
Definition	Low serum magnesium levels, typically below **0.75 mmol/L (1.8 mg/dL)**.
Causes	- **Gastrointestinal Losses**: Diarrhea, vomiting, malabsorption (e.g., Crohn's disease), chronic laxative use - **Renal Losses**: Diuretics (loop, thiazide), hyperaldosteronism, medications (e.g., aminoglycosides) - **Alcoholism**: Poor intake, GI losses, and renal wasting - **Endocrine Disorders**: Hyperparathyroidism, hyperthyroidism, diabetic ketoacidosis (DKA)
Pathophysiology	Magnesium is essential for cellular functions, ATP production, and neuromuscular stability. Low magnesium can lead to **cellular excitability** and **electrolyte imbalances** (e.g., hypokalemia, hypocalcemia).
Clinical Features	- **Neuromuscular**: Tremors, muscle cramps, tetany, seizures - **Cardiovascular**: Palpitations, arrhythmias (e.g., Torsades de Pointes), prolonged QT interval - **Metabolic**: Hypocalcemia and hypokalemia often coexist due to disrupted ion transport
Diagnosis	- Serum magnesium level < 0.75 mmol/L - **Associated Electrolyte Imbalances**: Low potassium and calcium due to coexisting electrolyte losses, often requiring further evaluation.
Management	- **Oral Magnesium Supplements**: For mild cases - **Magnesium oxide**: 250-400 mg orally 1-2 times daily - **Magnesium citrate**: 240 mg orally once daily - **IV Magnesium Sulfate**: For severe or symptomatic cases - **Dose**: 1-2 grams over 15-60 minutes for acute replacement, repeated every 6-12 hours as needed - **Treat Underlying Cause**: Address GI losses, adjust medications, manage alcohol use if needed
Key Points for MRCP	1. Common in alcoholics and those on diuretics. 2. Symptoms include **muscle cramps**, **tetany**, and **arrhythmias**. 3. Hypokalemia and hypocalcemia often coexist, requiring correction alongside magnesium.

Replace magnesium before correcting hypokalaemia.

Hypomagnesaemia prevents potassium absorption

Hypermagnesemia

Category	Details
Definition	Elevated serum magnesium levels, typically above 1.1 mmol/L (2.6 mg/dL).
Causes	- **Renal Insufficiency**: Most common cause, due to reduced excretion of magnesium - **Excessive Intake**: High doses from antacids, laxatives, or IV infusions - **Medications**: Magnesium-containing drugs or those reducing renal magnesium excretion (e.g., lithium) - **Other Causes**: Adrenal insufficiency, hypothyroidism, tumor lysis syndrome
Pathophysiology	High magnesium levels depress neuromuscular and cardiac function by inhibiting calcium and potassium channels, causing muscular and cardiovascular symptoms.
Clinical Features	- **Mild**: Often asymptomatic - **Moderate to Severe**: - **Neuromuscular**: Muscle weakness, hyporeflexia, lethargy - **Cardiovascular**: Hypotension, bradycardia, prolonged PR and QRS intervals, risk of cardiac arrest - **Respiratory Depression**: In severe cases due to impaired muscle function
Diagnosis	Elevated serum magnesium levels, potentially with hyperkalemia and hypercalcemia in cases of renal failure.
Management	- **Stop Magnesium Intake**: Discontinue magnesium-containing medications or supplements - **IV Calcium Gluconate**: Antagonizes effects on heart and muscles in acute cases - **Hydration and Diuretics**: IV fluids and loop diuretics to promote excretion in those with normal renal function - **Dialysis**: Required for severe cases, especially in renal failure
Key Points for MRCP	1. Renal failure is the main cause. 2. Symptoms include neuromuscular and cardiovascular depression. 3. Treatment includes stopping magnesium, IV calcium for acute symptoms, and dialysis if severe.

Vitamin D deficiency

Definition

- A condition where serum 25-hydroxyvitamin D levels fall below the optimal range, typically defined as levels under **20 ng/mL (50 nmol/L)**.

Causes

1. **Inadequate Sun Exposure**:
   - Limited outdoor activities, high latitude regions, sunscreen use.
2. **Dietary Insufficiency**:
   - Low intake of vitamin D-rich foods (e.g., fish, fortified dairy).

3. **Malabsorption Disorders**:
   - Conditions like **celiac disease**, **Crohn's disease**, and **bariatric surgery** affecting vitamin D absorption.
4. **Liver or Kidney Disease**:
   - Impaired conversion of vitamin D to its active form.
5. **Medications**:
   - Drugs like glucocorticoids, anticonvulsants, and rifampin can decrease vitamin D levels.

Pathophysiology

- Vitamin D is essential for **calcium and phosphate homeostasis** and **bone mineralization**. Deficiency leads to reduced intestinal calcium absorption, secondary hyperparathyroidism, and increased bone resorption, leading to weakened bones.

Clinical Features

- **Skeletal Symptoms**:
  - Bone pain, muscle weakness, and in severe cases, osteomalacia in adults or rickets in children.
- **Fracture Risk**:
  - Increased susceptibility to fractures due to bone demineralization.
- **Muscle Weakness**:
  - Particularly in proximal muscles, which may lead to difficulty in standing and walking.

Diagnosis

- **Serum 25-hydroxyvitamin D levels** (best marker for deficiency).
- Additional tests: Calcium, phosphate, PTH, and alkaline phosphatase to assess bone health and secondary hyperparathyroidism.

Management

1. **Vitamin D Supplementation**:
   - **Mild Deficiency**: 800-1,000 IU of vitamin D3 daily.
   - **Severe Deficiency**: High-dose vitamin D (50,000 IU weekly) for 6-8 weeks, followed by maintenance dosing.
2. **Calcium Supplementation**:
   - Often added to support bone health.
3. **Address Underlying Causes**:
   - Treat malabsorption or adjust medications impacting vitamin D levels.

Hypophosphatasemia

Definition

- Low serum phosphate levels, typically below 0.8 mmol/L (2.5 mg/dL), which may impair bone mineralization and cellular function.

Causes

1. **Inadequate Phosphate Intake**:
   - Poor dietary intake or malnutrition.
2. **Excessive Loss of Phosphate**:
   - **Hyperparathyroidism**: Increased renal phosphate excretion.
   - **Renal Tubular Disorders**: e.g., Fanconi syndrome, causing renal phosphate wasting.
3. **Shift of Phosphate into Cells**:
   - **Refeeding Syndrome**: Rapid intracellular phosphate uptake after malnutrition.
   - **Respiratory Alkalosis**: Increases cellular uptake of phosphate.
4. **Vitamin D Deficiency or Resistance**:
   - Impaired phosphate absorption from the gastrointestinal tract.

Pathophysiology

- Phosphate is critical for cellular energy (ATP) and bone mineralization. Low levels can result in impaired cellular function, energy production, and skeletal integrity.

Clinical Features

- **Mild Hypophosphatemia**: Often asymptomatic.
- **Moderate to Severe Hypophosphatemia**:
  - **Muscle Weakness**: Especially in respiratory and proximal muscles.
  - **Bone Pain** and risk of osteomalacia or rickets (in chronic cases).
  - **Neurological Symptoms**: Confusion, irritability, or seizures.
  - **Cardiovascular Dysfunction**: Potential arrhythmias and heart failure in severe cases.

Diagnosis

- Low serum phosphate level.
- Evaluation of underlying causes, including PTH levels, renal function, and vitamin D status.

Management

1. **Oral Phosphate Supplementation**:
   - For mild cases, typically 250-500 mg of phosphate per day.
2. **Intravenous Phosphate**:
   - For severe or symptomatic cases, especially if levels are below 0.3 mmol/L (1.0 mg/dL).
3. **Treat Underlying Cause**:
   - Correct hyperparathyroidism, renal tubular disorders, or vitamin D deficiency.

Key Points for MRCP Candidates

1. **Common causes** include hyperparathyroidism, refeeding syndrome, and renal tubular disorders.
2. **Symptoms** arise in moderate to severe cases and include **muscle weakness, bone pain, and neurocognitive issues.**

Hyperphosphataemia

Definition

- Elevated serum phosphate levels, typically above 1.45 mmol/L (4.5 mg/dL).

Causes

1. **Renal Failure** (most common):
    - Decreased phosphate excretion due to impaired kidney function.
2. **Hypoparathyroidism**:
    - Reduced parathyroid hormone (PTH) leads to decreased renal phosphate excretion.
3. **Excessive Phosphate Intake**:
    - High dietary phosphate, especially with use of phosphate-containing laxatives or supplements.
4. **Cellular Release**:
    - Tumor lysis syndrome, rhabdomyolysis, or hemolysis causing intracellular phosphate release.
5. **Vitamin D Toxicity**:
    - Increased gastrointestinal phosphate absorption.

Pathophysiology

- Excess phosphate can combine with calcium, forming calcium-phosphate complexes, which may deposit in tissues, leading to calcification, particularly in **soft tissues and blood vessels**.

Clinical Features

- **Asymptomatic** in mild cases.
- **Hypocalcemia symptoms** due to calcium-phosphate binding, leading to **muscle cramps, tetany, and numbness**.
- **Calcification** of soft tissues, joints, and vascular system in chronic cases.

Diagnosis

- Elevated serum phosphate levels.
- Associated findings may include **low serum calcium** (secondary to calcium-phosphate binding) and high **PTH** in secondary hyperparathyroidism (e.g., renal failure).

Management

1. **Dietary Phosphate Restriction**:
    - Recommended in chronic kidney disease (CKD) patients, typically limiting intake to 800-1000 mg/day.
2. **Phosphate Binders**:
    - **Non-calcium-containing binders**: Sevelamer, lanthanum.
    - **Calcium-containing binders**: Calcium acetate or calcium carbonate (used cautiously due to risk of hypercalcemia).
3. **Dialysis**:
    - For severe or refractory cases in CKD, to assist in phosphate removal.
4. **Calcimimetics**:
    - Cinacalcet for secondary hyperparathyroidism in CKD patients to reduce PTH and indirectly lower phosphate.

Key Points for MRCP Candidates

1. **Renal failure** is the primary cause of hyperphosphatemia.
2. **Soft tissue calcification** risk increases in chronic hyperphosphatemia, especially in CKD.
3. **Phosphate binders** are essential in managing phosphate levels in CKD.
4. **Hyperphosphatemia** can lead to **hypocalcemia** and should be monitored in patients with renal or endocrine disorders.

Hyperparathyroidism

Classification of Hyperparathyroidism

Type	PTH	Serum Ca	Serum Phos	Causes
Primary	High	High	Low	Parathyroid adenoma, hyperplasia, carcinoma
Secondary	High	Normal/Low	High	Chronic renal failure (CRF), vitamin D deficiency, malnutrition
Tertiary	High	High	High	Chronic renal disease with hyperplasia leading to autonomous secretion of PTH

Primary Hyperparathyroidism (PHPT)

- **Epidemiology**: Most common cause of hypercalcemia (0.1% prevalence, higher in females aged 50-60).
- **Causes**: 80% solitary adenoma, 15% hyperplasia, 4% multiple adenomas, 1% carcinoma.
- **Pathophysiology**: Overproduction of PTH leads to increased calcium release from bones, renal calcium reabsorption, and phosphate excretion.
- **Clinical Features**:
  - **Bones**: Bone pain, pseudogout.
  - **Stones**: Nephrolithiasis, nephrocalcinosis.
  - **Abdominal Groans**: Constipation, nausea, gastric ulcers, acute pancreatitis.
  - **Psychiatric Moans**: Depression, fatigue, anxiety.
  - **Cardiovascular**: Hypertension, LV hypertrophy, shortened QT interval.
- **Investigations**:
  - Elevated serum calcium, low phosphate, high/normal PTH.
  - **Imaging**: Technetium (99mTc) sestamibi scan for tumour localization.
- **Treatment**:
  - **Surgery**: Parathyroidectomy in symptomatic patients or those meeting specific criteria.
  - **Complications**: **Hungry bone syndrome** post-surgery with severe hypocalcemia.

Secondary Hyperparathyroidism

- **Definition**: PTH overproduction due to low calcium, often secondary to chronic kidney disease.
- **Pathophysiology**: Renal impairment → reduced vitamin D production & phosphate excretion → hypocalcemia & hyperphosphatemia → elevated PTH.
- **Features**: Low serum calcium, high phosphate, elevated PTH, high alkaline phosphatase.
- **Management**:
  - **Hyperphosphatemia**: Dietary restriction, phosphate binders (Sevelamer, Ferric citrate), or tenapanor in resistant cases.

- o **Hypocalcemia & Vitamin D Deficiency**: Calcium and vitamin D supplementation.
- o **Elevated PTH**: Calcimimetics (e.g., cinacalcet for dialysis patients), calcitriol for PTH reduction.
- **Treatment**: Renal transplant is optimal; parathyroidectomy for severe cases.

Tertiary Hyperparathyroidism

- **Pathophysiology**: Prolonged secondary hyperparathyroidism (e.g., in CKD) leads to autonomous PTH secretion by hyperplastic glands.
- **Features**: Elevated serum calcium and phosphate, refractory to correction.
- **Management**: Primarily **surgical** (parathyroidectomy); **cinacalcet** may be used in patients unfit for surgery.

Hypoparathyroidism

Overview

- **Causes**: Postoperative (most common), autoimmune, infiltrative diseases (e.g., Wilson's, hemochromatosis), congenital (DiGeorge syndrome).
- **Features**: Hypocalcemia (tetany, seizures), hyperphosphatemia, low/inappropriately normal PTH.
- **Treatment**: Calcium and vitamin D supplementation, recombinant PTH if needed.

Pseudohypoparathyroidism

- **Definition**: End-organ resistance to PTH due to defective Gs protein α subunit.
- **Inheritance**: Autosomal dominant, inherited maternally (GNAS gene).
- **Types**:
  - o Type I: Complete receptor defect.
  - o Type II: Receptor is intact, defect lies in signaling.
- **Features**: Albright hereditary osteodystrophy (short stature, brachydactyly, obesity) and symptoms of hypocalcemia despite high PTH.
- **Diagnostics**: Urinary cAMP and phosphate levels post-PTH infusion.
- **Management**: Calcium and vitamin D supplementation.

Pseudo-Pseudohypoparathyroidism

- Similar phenotype to pseudohypoparathyroidism but **normal calcium, PTH, and phosphate** levels.
- Inherited from the father (as opposed to pseudohypoparathyroidism, which is maternally inherited).

Osteomalacia

Pathophysiology: decreased mineral content but normal bony tissue.

Causes & Risk factors

- **Vitamin D deficiency** (most common) e.g. malabsorption, lack of sunlight, diet, inherited Vitamin D resistant
- Renal failure, Liver disease, e.g. cirrhosis
- Drug induced e.g. anticonvulsants
- **Mercury poisoning** or any heavy metal poisoning causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.
- Ethnic origin
  - ⇨ More common in patients of **South Asian origin**, particularly those who have a cultural tendency to spend more time inside or cover themselves up so that cholesterol cannot be converted to vitamin D in the skin.
  - ⇨ More common in ethnic groups who are **dark-skinned**
  - ⇨ **Asians** who eat chapattis are also at risk, as the phytic acid in the chapattis chelates vitamin D and calcium

Features

- Bone pain and tenderness (particularly around the hips and lower back)
- Proximal myopathy: muscle weakness, difficulty walking, and a waddling gait.

Investigation: ↓↓ Ca ↓↓ P ↓↓ vit D + ↑↑ ALP

- Low calcium, phosphate & vitamin D
- Raised alkaline phosphatase
- Elevated Serum PTH
- Plain x-ray of spine and long bones: → translucent bands (**Looser's zones: Linear areas of low density**) (pseudofractures)

Treatment: calcium with vitamin D tablets (50,000 international units of vitamin D3 orally once per week for 6 – 8 to weeks, followed by a maintenance dose, 600 to 800 international units of vitamin D3 daily) + calcium intake of 1000 to 1200 mg per day.

Osteoporosis

Definition

- Osteoporosis is a systemic skeletal disorder characterized by reduced bone density and deterioration in bone microarchitecture, leading to increased fragility and fracture risk. It is often asymptomatic until a fracture occurs, emphasizing the need for proactive screening and prevention strategies.

Risk Factors

- **Age and Gender**: Common in postmenopausal women and men over 50 years.
- **Medical Conditions**: Rheumatoid arthritis, chronic liver/kidney disease, hyperthyroidism, and malabsorption disorders.
- **Androgen deficiency** in men (primary or secondary)
- **Medications**: Glucocorticoids (≥7.5 mg/day for 3 months), aromatase inhibitors, and proton pump inhibitors.
- **Lifestyle Factors**: Smoking, alcohol consumption (>3 units/day), and insufficient calcium or vitamin D intake.

Diagnosis

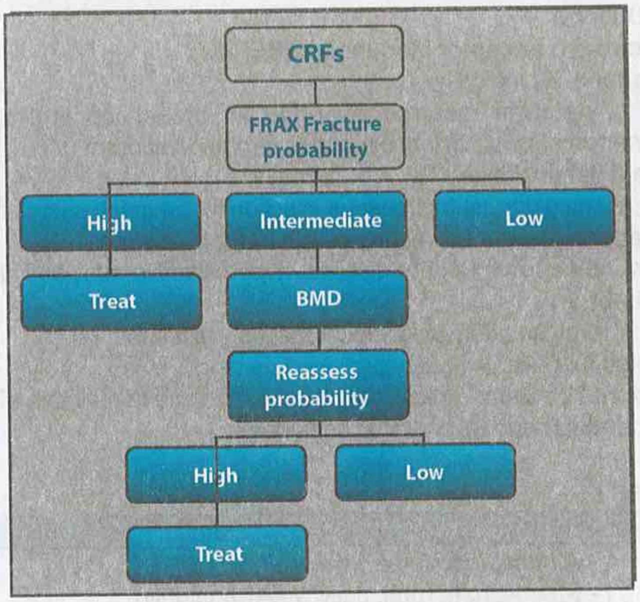
Step 1: Risk Assessment

- Use the **FRAX tool** (https://fraxplus.org) to estimate the 10-year risk of fractures.
- **Indications for screening** include:
  - Postmenopausal women and men ≥50 years.
  - Long-term glucocorticoid therapy (>7.5 mg prednisolone for 3 months).
  - History of fractures or conditions affecting bone health (e.g., rheumatoid arthritis, hyperthyroidism)

.

Step 2: Diagnostic Testing

- **DEXA Scan**: Measures Bone Mineral Density (BMD).
  - **T-Score Interpretation**:
    - ≥ -1.0: Normal
    - -1.0 to -2.5: Osteopenia
    - ≤ -2.5: Osteoporosis
- **Additional Tests**:
  - Serum calcium, vitamin D, thyroid function, and renal/liver function to rule out secondary causes



Management

Lifestyle Modifications

- Adequate **Calcium and Vitamin D** intake:
  - **Calcium**: 1200 mg/day
  - **Vitamin D**: 800-1000 IU/day
- Regular **weight-bearing and resistance exercises**.
- **Smoking cessation** and **limit alcohol** intake (<3 units/day).
- **Fall prevention** strategies in older adults

Pharmacologic Treatment

Indications for Drug Therapy:

- T-score ≤ -2.5 (osteoporosis diagnosis).
- History of fragility fracture.
- High fracture risk (based on FRAX).
- Glucocorticoid use ≥7.5 mg/day for 3 months or more.

First-line: Bisphosphonates

- **Alendronate**: 70 mg weekly or 10 mg daily (oral).
- **Risedronate**: 35 mg weekly or 5 mg daily (oral).
- **Zoledronic acid**: 5 mg IV once annually.
- **Contraindications**: Severe renal impairment (GFR <30-35 ml/min), esophageal abnormalities.
- **Adverse effects**: GI upset, osteonecrosis of the jaw, hypocalcemia

Second-line: Denosumab

- **Dose**: 60 mg subcutaneous injection every 6 months.
- **Mechanism**: Inhibits RANKL, preventing osteoclast maturation.
- **Contraindications**: Hypocalcemia (correct calcium levels before initiation).
- **Special Considerations**: Risk of rebound vertebral fractures if stopped abruptly; follow with bisphosphonate treatment

Other Treatment Options

1. **Selective Estrogen Receptor Modulators (SERMs)**:
   - **Raloxifene**: 60 mg daily.
   - Used for **vertebral fracture prevention** and **breast cancer prophylaxis**.
   - **Contraindications**: History of venous thromboembolism (VTE), liver disease.
2. **Teriparatide** (PTH analogue):
   - **Dose**: 20 mcg daily subcutaneous injection for 24 months (lifetime limit).
   - **Indications**: Severe osteoporosis with multiple fractures.
   - **Contraindications**: Paget's disease, hypercalcemia, previous skeletal radiation.
3. **Romosozumab**:
   - **Dose**: 210 mg monthly (two subcutaneous injections).
   - Indicated for patients at very high fracture risk.
   - **Duration**: 12 months, followed by bisphosphonate to maintain effect
   - ⇨ **Contraindication:** severe renal impairment

Bisphosphonates

Category	Details
Agents	- **Alendronate** (oral, weekly) - **Risedronate** (oral, daily/weekly/monthly) - **Ibandronate** (oral, monthly or IV every 3 months) - **Zoledronic Acid** (IV, annually)
Mechanism of Action	Inhibition of Osteoclast-Mediated Bone Resorption
Uses	- First-line treatment for **osteoporosis** in postmenopausal women, men, and glucocorticoid-induced osteoporosis - **Paget's disease of bone** - **Hypercalcemia of malignancy**

Administration	- **Oral formulations**: Take with a full glass of water on an empty stomach; remain upright for 30-60 minutes to prevent esophagitis - **IV formulations**: Administered once yearly (Zoledronic Acid) or every 3 months (Ibandronate)
Side Effects	- **Gastrointestinal**: Esophagitis, dyspepsia, nausea (more common with oral forms) - **Musculoskeletal**: Bone, joint, or muscle pain - **Rare**: Osteonecrosis of the jaw, atypical femoral fractures (with long-term use) - **Renal**: Risk of nephrotoxicity, especially with IV forms
Contraindications	- **Oral bisphosphonates**: Patients with esophageal disorders (e.g., achalasia, esophageal stricture) - **All bisphosphonates**: Hypocalcemia, severe renal impairment (eGFR < 30-35 mL/min)
Specific Notes	- Ensure **adequate calcium and vitamin D** supplementation - **Drug holiday** may be considered after 3-5 years of use to reduce long-term risks - Regular **dental check-ups** recommended due to the risk of jaw osteonecrosis, particularly in patients receiving IV bisphosphonates or with invasive dental procedures

Denosumab

Category	Details
Mechanism of Action	- **RANK Ligand Inhibitor**: Denosumab is a monoclonal antibody that inhibits RANKL, reducing osteoclast formation and activity, thereby decreasing bone resorption.
Indications	- **Postmenopausal osteoporosis** in women at high risk of fracture - **Osteoporosis in men** at high risk of fracture - **Glucocorticoid-induced osteoporosis** - **Bone loss** due to androgen deprivation in prostate cancer or aromatase inhibitor therapy in breast cancer
Administration	- Given as a **subcutaneous injection** every **6 months** (60 mg)
Side Effects	- **Hypocalcemia**: Most common, especially in patients with renal impairment - **Skin reactions**: Dermatitis, eczema, and rashes - **Musculoskeletal pain** - **Rare**: Osteonecrosis of the jaw (ONJ) and atypical femur fractures
Contraindications	- **Hypocalcemia**: Must be corrected before initiating treatment - Known hypersensitivity to denosumab or its components
Specific Notes	- **Supplementation** with calcium and vitamin D is essential throughout treatment - **Rebound bone loss**: Rapid bone density loss can occur if treatment is stopped abruptly, so transitioning to another osteoporosis therapy is recommended if discontinuing denosumab - Requires regular **dental exams** due to risk of ONJ, especially if invasive dental procedures are needed

Selective Estrogen Receptor Modulators (SERMs)

Category	Details
Examples	- **Raloxifene** - **Bazedoxifene** (often combined with conjugated estrogens in postmenopausal women)
Mechanism of Action	- SERMs act as **estrogen agonists** on bone, reducing osteoclast activity and bone resorption. - Act as **estrogen antagonists** on breast and uterine tissue, lowering the risk of estrogen-dependent cancers.
Indications	- **Postmenopausal osteoporosis**: Reduces vertebral fracture risk but not hip fractures. - **Breast cancer prevention**: Raloxifene is used in high-risk postmenopausal women to lower the risk of invasive breast cancer.
Administration	- **Oral**: Typically once daily, e.g., raloxifene 60 mg per day.
Side Effects	- **Hot flashes** - **Leg cramps** - **Increased risk of venous thromboembolism (VTE)** - Rarely, increased risk of fatal stroke in certain populations (not suitable for women with a history of stroke).
Contraindications	- **History of venous thromboembolism** (VTE) - **Pregnancy and breastfeeding** - Severe hepatic impairment
Specific Notes	- SERMs are most effective for **vertebral fracture prevention** and are generally used in women at risk for both osteoporosis and breast cancer. - They are not first-line for osteoporosis but may be suitable for those unable to tolerate other treatments or those at high breast cancer risk.

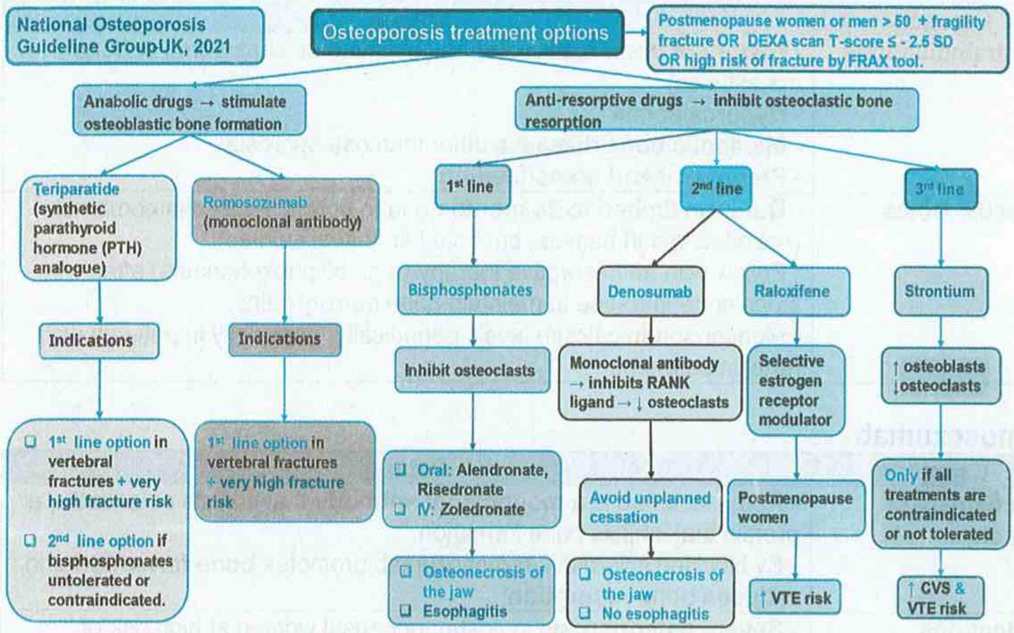
Teriparatide

Category	Details
Mechanism of Action	- Teriparatide is a **recombinant form of parathyroid hormone (PTH)** that stimulates osteoblast activity, leading to **increased bone formation**.
Indications	- **Severe osteoporosis** in postmenopausal women and men at high risk for fracture - **Glucocorticoid-induced osteoporosis** in patients at high fracture risk
Administration	- **Subcutaneous injection** daily (20 mcg) for up to 24 months (2 years), after which alternative therapy is recommended
Side Effects	- **Hypercalcemia** and hypercalciuria - **Orthostatic hypotension** (typically after initial doses) - **Nausea** and leg cramps - **Rare**: Risk of osteosarcoma (observed in animal studies)

Category	Details
Contraindications	- **History of bone malignancies** (including osteosarcoma or bone metastases) - **Hypercalcemia** - **Metabolic bone diseases** other than osteoporosis - **Pregnancy and breastfeeding**
Specific Notes	- **Duration limited to 24 months** due to potential osteosarcoma risk (not observed in humans but noted in animal studies). - Follow with antiresorptive therapy (e.g., bisphosphonates) after stopping teriparatide to maintain bone density gains. - Monitor serum calcium levels periodically, especially in patients with renal impairment.

Romosozumab

Category	Details
Mechanism of Action	- Romosozumab is a **monoclonal antibody** that inhibits **sclerostin**, a protein that inhibits bone formation. - By blocking sclerostin, romosozumab promotes **bone formation** and **reduces bone resorption**.
Indications	- **Severe osteoporosis** in postmenopausal women at high risk of fracture, especially those who fail or cannot tolerate other treatments
Administration	- **Subcutaneous injection** once monthly (210 mg) for a maximum of **12 months**
Side Effects	- **Injection site reactions** - **Arthralgia** and muscle pain - **Hypocalcemia** (especially in patients with renal impairment) - **Cardiovascular risk**: Increased risk of myocardial infarction and stroke observed in some studies
Contraindications	- **History of myocardial infarction (MI) or stroke** - **Hypocalcemia** (must be corrected before initiating treatment)
Specific Notes	- Treatment is limited to **12 months** due to diminishing efficacy with longer use. - **Follow-up with antiresorptive therapy** (e.g., bisphosphonates) is recommended after discontinuation to maintain bone density gains. - **Calcium and vitamin D supplementation** are advised during treatment to mitigate hypocalcemia risk.


National Osteoporosis Guideline GroupUK, 2021
Osteoporosis treatment options
Postmenopause women or men > 50 + fragility fracture OR DEXA scan T-score ≤ - 2.5 SD OR high risk of fracture by FRAX tool.
Anabolic drugs → stimulate osteoblastic bone formation
Anti-resorptive drugs → inhibit osteoclastic bone resorption
Teriparatide (synthetic parathyroid hormone (PTH) analogue)
Romosozumab (monoclonal antibody)
Indications
Indications
1st line option in vertebral fractures + very high fracture risk
2nd line option if bisphosphonates untolerated or contraindicated.
1st line option in vertebral fractures + very high fracture risk
1st line
2nd line
3rd line
Bisphosphonates
Denosumab
Raloxifene
Strontium
Inhibit osteoclasts
Monoclonal antibody → inhibits RANK ligand → ↓ osteoclasts
Selective estrogen receptor modulator
↑ osteoblasts ↓osteoclasts
Oral: Alendronate, Risedronate
IV: Zoledronate
Avoid unplanned cessation
Postmenopause women
Only if all treatments are contraindicated or not tolerated
Osteonecrosis of the jaw
Esophagitis
Osteonecrosis of the jaw
No esophagitis
↑ VTE risk
↑ CVS & VTE risk

Adrenal disorders

Primary hyperaldosteronism

Definition

- A condition characterized by **excess production of aldosterone** from the adrenal glands, leading to **hypertension** and **hypokalemia**.

Epidemiology

- Primary hyperaldosteronism accounts for approximately **5-10% of cases of hypertension** and is the most common cause of secondary hypertension.

Pathophysiology

- Aldosterone excess results in:
  - **Increased sodium retention** and **water reabsorption** → volume expansion and hypertension.
  - **Increased potassium excretion** → hypokalemia and metabolic alkalosis.

Causes

1. **Aldosterone-producing adenoma** (Conn's syndrome) – most common cause.
2. **Bilateral adrenal hyperplasia.**
3. **Unilateral adrenal hyperplasia** or **adrenocortical carcinoma** (rare).
4. **Familial hyperaldosteronism** (rare, genetic disorder).

Clinical Features

- **Hypertension**: Often resistant to standard antihypertensive therapy.
- **Hypokalemia**: Fatigue, muscle weakness, cramps, and in severe cases, palpitations or arrhythmias.
- **Metabolic Alkalosis**: Due to excess potassium loss.

Diagnostic Evaluation

1. **Screening**:
   - **Plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio (ARR)**: Elevated ratio is suggestive.
2. **Confirmatory Tests** (if ARR is elevated):
   - **Saline infusion test**, **oral salt loading**, or **fludrocortisone suppression test**.
3. **Localization**:
   - **Adrenal CT/MRI**: Identifies adrenal adenomas or hyperplasia.
   - **Adrenal vein sampling** (AVS): Differentiates unilateral (adenoma) from bilateral (hyperplasia) disease, especially if surgery is considered.

Treatment

Condition	Treatment Options
Aldosterone-producing adenoma (Unilateral)	**Surgical resection** (adrenalectomy) – preferred for adenoma or unilateral hyperplasia.
Bilateral adrenal hyperplasia	**Medical therapy**: - **Mineralocorticoid receptor antagonists** (e.g., spironolactone, eplerenone). - **Amiloride** as an alternative if spironolactone is not tolerated.
Lifestyle modifications	Dietary sodium restriction and potassium supplementation (if hypokalemia is present).

Key Points for MRCP

- Primary hyperaldosteronism should be suspected in cases of **resistant hypertension** and **unexplained hypokalemia**.
- **ARR** is the preferred screening test; further confirmatory and imaging studies are warranted for diagnosis.
- **Surgical resection** is curative for unilateral causes; **medical therapy** is the mainstay for bilateral disease.

Aldosterone-to-Renin Ratio (ARR)

Parameter	Details
Definition	Ratio of **plasma aldosterone concentration (PAC)** to **plasma renin activity (PRA)**, used as a screening test for **primary hyperaldosteronism.**
Normal Range	ARR < 20 ng/dL per ng/mL/hour (cutoffs may vary based on assay and units)
Interpretation	- **High ARR** (typically > 20–40) with elevated PAC suggests primary hyperaldosteronism. - **Low ARR** indicates other causes of hypertension.
Indications for Testing	- **Resistant hypertension** - **Hypokalemia** - Hypertension with **adrenal incidentaloma** - Early-onset hypertension or family history of primary hyperaldosteronism
Pre-test Preparation	- **Pause medications**: Certain antihypertensives (e.g., spironolactone, eplerenone) may interfere with ARR results. - **Adequate salt intake** is recommended before testing.
Confirmatory Testing	Elevated ARR is followed by confirmatory tests (e.g., **saline infusion test**) to diagnose primary hyperaldosteronism.
Limitations	- ARR can be affected by medications, diet, and posture. - False negatives may occur in mild primary hyperaldosteronism.
Key Points for MRCP	- High ARR suggests primary hyperaldosteronism, a common secondary hypertension cause. - Confirmatory testing is essential for diagnosis following an elevated ARR.

Effect of Drugs on Aldosterone-to-Renin Ratio (ARR)

Effect of ARR	Drugs
No Effect on ARR	Alpha-blockers, Calcium channel blockers, Hydralazine
False Negative result: ↑ Renin, ↓ Aldosterone	ACE inhibitors, ARBs (**in practice ARR** can be assessed without stopping these agents. It may **improve the sensitivity of the test.**)
False Negative result↑ Both renin and aldosterone	Diuretics, Aldosterone Receptor Antagonists
False Positive result↓ Renin	Beta-blockers, Methyldopa

Important Considerations

- **Washout Period**: Discontinue most medications **4-6 weeks** prior to ARR testing; beta-blockers and diuretics may need a shorter washout (2 weeks).
- **Clinical Judgment**: Patients with severe hypertension may need continuation of some medications; adjust based on risk and use alternatives like **verapamil**, **diltiazem**, or **alpha-blockers** where feasible.
- **Potassium Levels**: Correct hypokalemia before doing ARR (because low potassium suppresses aldosterone secretion), especially when discontinuing potassium-sparing drugs.

Saline Infusion Test (SIT) for Confirming Primary Hyperaldosteronism

Parameter	Details
Purpose	To confirm primary hyperaldosteronism by assessing aldosterone response to saline infusion (aldosterone levels should suppress in normal physiology).
Procedure	- Patient rests in a seated position. - Administer **2 litres of normal saline** intravenously over **4 hours**.
Pre-test Preparation	- **Hold interfering medications** (e.g., diuretics, ACE inhibitors) 2-6 weeks prior. - **Adequate salt intake** for at least 3 days before test.
Interpretation	- **Positive for primary hyperaldosteronism**: Post-infusion plasma aldosterone >10 ng/dL (suggests autonomous aldosterone secretion). - **Negative**: Aldosterone <5 ng/dL
Advantages	Reliable for diagnosing primary hyperaldosteronism in patients with high pre-test probability.
Limitations	- False positives may occur in patients with severe hypertension. - May not be suitable for those with fluid overload risk (e.g., heart failure, kidney disease).

Secondary Hyperaldosteronism

Definition

- Secondary hyperaldosteronism refers to excessive aldosterone secretion caused by increased stimulation of the renin-angiotensin-aldosterone system (RAAS).

Pathophysiology

- Occurs due to reduced effective circulating blood volume, leading to activation of RAAS.
- Elevated renin levels stimulate the adrenal glands to produce more aldosterone.

Causes

- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal artery stenosis
- Dehydration
- Diuretic use

Clinical Features

- Mild hypertension
- Hypokalaemia (occasional)
- Polyuria and muscle weakness (if hypokalaemia is severe)
- Absence of oedema, which helps distinguish it from primary hyperaldosteronism.

Complications

- Persistent hypokalaemia
- Metabolic alkalosis
- Increased cardiovascular risk due to elevated blood pressure

Diagnosis

- **Plasma renin and aldosterone levels**: Both renin and aldosterone are elevated.
- **Aldosterone-to-renin ratio (ARR)**: Normal or low.
- **Electrolytes**: May show hypokalaemia and metabolic alkalosis.
- **Imaging**: Ultrasound or CT to assess for renal artery stenosis if indicated.

Treatment

- **Address the underlying cause**: Manage the primary condition, such as heart failure or cirrhosis.
- **Aldosterone antagonists** (e.g., spironolactone, eplerenone) for symptomatic control.
- **ACE inhibitors or ARBs** to reduce RAAS activity.
- **Diuretics** to manage fluid overload if necessary.

Spironolactone

- **Mode of action**: Aldosterone receptor antagonist, reducing sodium reabsorption and potassium excretion.
- **Dose**: 25–100 mg daily, adjusted based on patient response and potassium levels.
- **Side effects**: Hyperkalaemia, gynecomastia, menstrual irregularities, and fatigue.
- **Contraindications**: Hyperkalaemia, renal impairment, and Addison's disease.

Key Points for MRCP

1. Differentiate secondary hyperaldosteronism from primary hyperaldosteronism by renin levels; both conditions have elevated aldosterone, but renin is high only in secondary hyperaldosteronism.
2. Common causes include conditions with reduced circulating blood volume or renal perfusion, such as heart failure and cirrhosis.

3. A **normal or low ARR** helps distinguish secondary hyperaldosteronism from primary hyperaldosteronism.
4. Treatment involves managing the underlying cause and using aldosterone antagonists for symptomatic relief.

Adrenal incidentaloma

Definition

- An adrenal incidentaloma is an **adrenal mass** ≥1 cm in size that is **incidentally discovered** during imaging studies for unrelated reasons.

Epidemiology

- Found in approximately 4-7% of abdominal imaging studies, with prevalence increasing with age.

Pathophysiology

- Most are benign; however, a subset may be functional (hormone-secreting) or malignant.

Classification

1. **Non-functioning**: Do not produce hormones and are often benign.
2. **Functioning**: Hormone-secreting and associated with conditions like:
    - **Cushing's syndrome** (cortisol excess)
    - **Phaeochromocytoma** (catecholamine excess)
    - **Primary hyperaldosteronism** (aldosterone excess)
    - **Androgen/Estrogen-secreting tumours** (rare)

Clinical Features

- **Non-functioning** incidentalomas are usually asymptomatic.
- **Functioning** tumours may present with symptoms related to hormone excess:
    - **Cushing's syndrome**: Weight gain, muscle weakness, hyperglycemia.
    - **Phaeochromocytoma**: Episodic hypertension, palpitations, sweating.
    - **Primary hyperaldosteronism**: Hypertension, hypokalemia.

Diagnostic Evaluation

1. **Hormonal Workup**:
    - **24-hour urinary cortisol** or **overnight dexamethasone suppression test** for Cushing's syndrome.
    - **Plasma metanephrines** for phaeochromocytoma.
    - **Plasma aldosterone-renin ratio** for primary hyperaldosteronism.
2. **Imaging**:
    - **CT/MRI**: Characterize size, shape, density, and malignancy risk.
    - **PET Scan**: Useful in suspected malignancy.

Imaging Findings in Adrenal Masses

Mass Type	CT Characteristics
Benign Adenoma	Homogeneous, lipid-rich, low attenuation
Phaeochromocytoma	Variable density, may have calcifications
Adrenocortical Carcinoma	Irregular, larger size (>4 cm), heterogeneous
Metastasis	Often bilateral, heterogenous

Management

1. **Non-functioning and <4 cm**:
   - Observation with periodic imaging and hormonal evaluation (typically at 6, 12, and 24 months).
2. **Functioning Tumours or >4 cm**:
   - Surgical resection due to malignancy risk or hormonal excess.
3. **Follow-Up**:
   - Regular imaging and hormone assessment for those under surveillance.

Key Points for MRCP

- Initial workup includes hormonal evaluation to rule out functional tumours.
- Size and imaging characteristics help guide management; masses >4 cm or with suspicious imaging features often require surgery.
- **CT** and **MRI** are primary imaging modalities; functional tumours may need further metabolic workup.

Adrenal Hyperandrogenism

Definition

- Adrenal hyperandrogenism refers to excessive production of androgens (e.g., testosterone, androstenedione, dehydroepiandrosterone sulfate [DHEA-S]) from the adrenal glands.

Pathophysiology

- It occurs due to increased adrenal androgen secretion, often related to enzyme defects, tumors, or hyperplasia of the adrenal cortex.
- Androgens produced by the adrenal glands are precursors to sex hormones and can affect secondary sexual characteristics and metabolic processes.

Causes

- **Congenital adrenal hyperplasia (CAH)**: Most commonly due to 21-hydroxylase deficiency.
- **Adrenal tumors**: Androgen-secreting adrenal adenomas or carcinomas.
- **Cushing's syndrome**: Associated with excess cortisol and sometimes increased adrenal androgens.
- **Polycystic ovary syndrome (PCOS)**: May involve mild adrenal hyperandrogenism.
- **Exogenous androgens**: Use of androgen supplements or anabolic steroids.

Clinical Features

- **Females**:
  - Hirsutism (excess hair growth)
  - Acne and seborrhoea
  - Male-pattern baldness
  - Virilization in severe cases (deep voice, clitoromegaly, increased muscle mass)
  - Menstrual irregularities or amenorrhea
- **Males**:
  - Prepubertal: Precocious puberty
  - Adults: No specific features, as androgen excess might not cause significant symptoms

Complications

- Virilization in females
- Infertility (in both genders)
- Psychological effects (e.g., body image concerns, anxiety, depression)
- Risk of adrenal carcinoma (if due to tumor)
- Metabolic syndrome, insulin resistance

Diagnosis

- **Hormonal assays:**
  - Elevated DHEA-S and androstenedione levels.
  - Testosterone may be raised (more common in females).
- **ACTH stimulation test:** Helps diagnose congenital adrenal hyperplasia.
- **Imaging:**
  - CT/MRI of adrenal glands if a tumor is suspected.
  - Pelvic ultrasound in females to assess ovaries and exclude PCOS.
- **24-hour urinary free cortisol:** If Cushing's syndrome is suspected.

Treatment

- **Address underlying cause:**
  - Surgical removal of adrenal tumors.
  - Glucocorticoid replacement for congenital adrenal hyperplasia.
- **Anti-androgens:**
  - **Spironolactone:** Aldosterone antagonist with anti-androgen properties.
  - **Flutamide:** Non-steroidal anti-androgen.
- **Oral contraceptives:** To regulate menstrual cycles and reduce androgen levels in females.
- **Glucocorticoids:** Low doses to suppress adrenal androgen production in CAH.
- **Lifestyle changes:** Weight loss may improve symptoms in overweight or obese patients with hyperandrogenism.

Key Points for MRCP Candidates

1. **Congenital adrenal hyperplasia** is the most common cause of adrenal hyperandrogenism, with 21-hydroxylase deficiency being the predominant enzyme defect.
2. **Hirsutism and virilization** are key clinical features in females.
3. **DHEA-S** is the best marker for adrenal androgen excess as it is produced exclusively by the adrenal glands.
4. Imaging is essential to rule out **adrenal tumors** if hormone levels are markedly elevated.
5. **Anti-androgens and oral contraceptives** are effective in managing symptoms, especially in females.

Congenital adrenal hyperplasia (CAH)

Definition

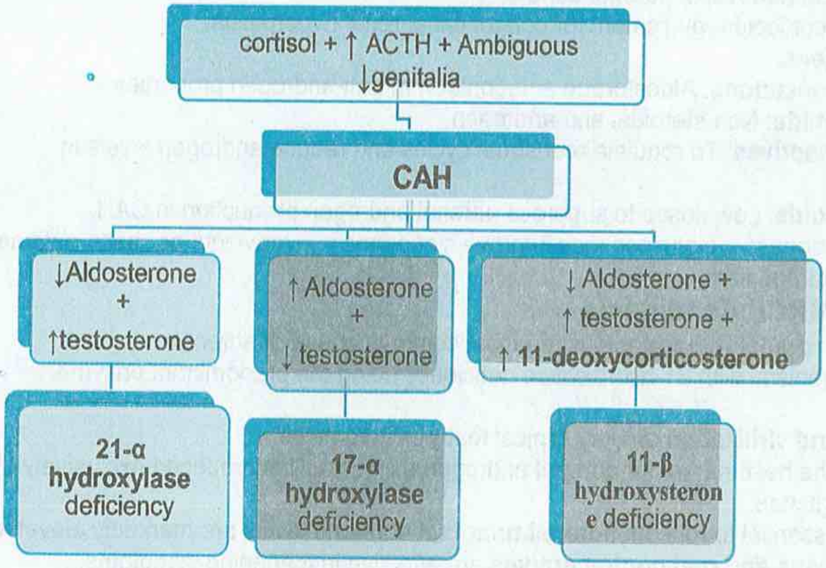
- A group of autosomal recessive genetic disorders affecting adrenal steroid synthesis, leading to cortisol deficiency.
- Most common form: **21-hydroxylase deficiency** (about 95% of cases), leading to excess androgen production and variable degrees of aldosterone deficiency.

Pathophysiology

- Enzyme deficiencies in the steroidogenesis pathway impair cortisol synthesis.
- **21-hydroxylase deficiency** leads to:
  - Reduced cortisol and potentially aldosterone.
  - Compensatory **ACTH increase** causing adrenal hyperplasia.
  - **Androgen excess** due to steroid precursors shunted toward androgen production.

Types of CAH

Type	Enzyme Deficiency	Hormonal Profile	Clinical Presentation
Classical	21-hydroxylase	Low cortisol, variable aldosterone, high androgens	Salt-wasting crisis, virilisation
Non-classical	21-hydroxylase	Mild cortisol deficiency, normal aldosterone, high androgens	Later onset, hirsutism, menstrual irregularities
Less Common Forms	11β-hydroxylase, 17α-hydroxylase	Variable cortisol and aldosterone, androgen excess or deficiency	Hypertension, virilisation, or hypogonadism



Clinical Features

- **Classic 21-hydroxylase deficiency**:
  - **Salt-wasting form**: Presents in infancy with dehydration, hyponatremia, hyperkalemia.
  - **Simple virilising form**: Androgen excess causes ambiguous genitalia in females, precocious puberty in males.
- **Non-classical 21-hydroxylase deficiency**:
  - Milder presentation with **androgen excess** leading to hirsutism, acne, menstrual irregularities, and infertility in females.
  - Usually presents later in life.

Complications

- **Adrenal crisis**: Risk in salt-wasting CAH with dehydration and electrolyte imbalances.
- **Growth disturbances**: Due to excess androgens and early puberty, leading to shorter final height.
- **Psychosocial impacts**: Ambiguous genitalia and early puberty can lead to psychological stress.

Diagnostic Criteria

- **Biochemical Testing**:
  - Elevated **17-hydroxyprogesterone** (especially after ACTH stimulation) in 21-hydroxylase deficiency.
  - Elevated **11-deoxycortisol** in 11β-hydroxylase deficiency.
- **Genetic Testing**: Confirms specific enzyme mutation.

Treatment

Treatment Goal	Management Approach
Hormone Replacement	**Hydrocortisone** for cortisol replacement **Fludrocortisone** if aldosterone is deficient
Suppress Androgen Excess	Glucocorticoids to reduce ACTH and androgen production
Salt Supplementation	Needed in infants with salt-wasting form to maintain sodium balance
Surgery	**Genital reconstructive surgery** for females with ambiguous genitalia (if needed)
Long-term Monitoring	Regular growth assessments, bone age monitoring, and psychological support

Key Points for MRCP

- **21-hydroxylase deficiency** is the most common form of CAH, presenting as salt-wasting, simple virilising, or non-classical.
- Diagnosis is based on **17-hydroxyprogesterone levels**; elevated levels post-ACTH stimulation are indicative.
- **Glucocorticoids and mineralocorticoids** are central to treatment, with the goal of managing cortisol deficiency and reducing androgen excess.

Comparison of 21-Hydroxylase, 11β-Hydroxylase, and 17α-Hydroxylase Deficiencies in Congenital Adrenal Hyperplasia (CAH)

Feature	21-Hydroxylase Deficiency	11β-Hydroxylase Deficiency	17α-Hydroxylase Deficiency
Enzyme Deficiency	21-hydroxylase	11β-hydroxylase	17α-hydroxylase
Hormonal Changes	↓ Cortisol, ↓ Aldosterone (salt-wasting type)	↓ Cortisol, ↑ Deoxycorticosterone (DOC), ↑ Androgens	↓ Cortisol, ↓ Androgens, ↑ Deoxycorticosterone (DOC)
Androgen Levels	**High** (due to shunting toward androgen pathway)	**High** (due to shunting toward androgen pathway)	**Low** (due to inhibited androgen synthesis)

Feature	21-Hydroxylase Deficiency	11β-Hydroxylase Deficiency	17α-Hydroxylase Deficiency
Mineralocorticoid Activity	- **Salt-wasting form**: Low aldosterone - **Simple virilising form**: Variable aldosterone	High (due to DOC acting as a mineralocorticoid)	High (due to DOC), leading to hypertension
Clinical Presentation	- **Salt-wasting crisis** in infancy (vomiting, dehydration, hyponatremia, hyperkalemia) - **Virilisation** in females - Precocious puberty in males	- **Hypertension** (due to excess DOC) - **Virilisation** in females	- **Hypertension and hypokalemia** - **Hypogonadism** in both genders (primary amenorrhea in females, ambiguous genitalia in males)
Blood Pressure	Normal or **low** (in salt-wasting type)	**High** (due to elevated DOC)	**High** (due to elevated DOC)
Electrolytes	**Hyponatremia, hyperkalemia** (in salt-wasting form)	**Normal** or hypokalemia	**Hypokalemia** (due to elevated DOC)
Key Diagnostic Markers	↑ 17-hydroxyprogesterone	↑ 11-deoxycortisol, ↑ DOC	↑ DOC, ↓ Sex steroids, ↓ Cortisol
Treatment	- **Glucocorticoids** to replace cortisol and reduce androgen excess - **Mineralocorticoids** (fludrocortisone) for salt-wasting form - **Salt supplementation** in infants	- **Glucocorticoids** to replace cortisol and lower DOC - Anti-hypertensives if needed	- **Glucocorticoids** to suppress ACTH - Anti-hypertensives if needed
Key Points for MRCP	- Most common CAH subtype - **Salt-wasting crisis** and virilisation common in severe cases	- Suspect in CAH with **hypertension and virilisation**	- Suspect in CAH with **hypertension and hypogonadism**

Glucocorticoid remediable aldosteronism (GRA)

Category	Details
Definition	Rare autosomal dominant disorder causing **aldosterone excess** that can be **suppressed by glucocorticoid therapy**.
Pathophysiology	Caused by a **genetic fusion of 11β-hydroxylase and aldosterone synthase genes**, leading to ACTH-regulated aldosterone production in the adrenal cortex.
Clinical Features	- **Early-onset hypertension** - **Hypokalemia** (may be mild) - **Metabolic alkalosis** - Family history of early hypertension or cerebrovascular events
Complications	- **Increased risk of cardiovascular events** - Potential for **renal damage** if left untreated
Diagnosis	- **Family history** of early hypertension - **Genetic testing** for CYP11B1/CYP11B2 fusion - **Suppressed renin** and **elevated aldosterone** levels
Treatment	- **Low-dose glucocorticoids** (e.g., dexamethasone or prednisone) to suppress ACTH - **Mineralocorticoid receptor antagonists** (e.g., spironolactone) if needed - **Blood pressure monitoring**
Key Points for MRCP	- GRA should be suspected in early-onset hypertension with a positive family history. - Glucocorticoids lower aldosterone by suppressing ACTH. - Confirm with genetic testing.

Pseudohyperaldosteronism

Category	Details
Definition	A condition with **hyperaldosteronism-like features** (hypertension, hypokalemia, metabolic alkalosis) but **normal or low aldosterone levels**.
Pathophysiology	Mimics aldosterone excess due to **non-aldosterone mechanisms**, commonly from **exogenous substances** or **genetic mutations** affecting mineralocorticoid receptors.
Causes	- **Licorice consumption** (contains glycyrrhetinic acid inhibiting 11β-HSD2 enzyme) - **Genetic disorders** (e.g., SAME) - **Drugs** (e.g., carbenoxolone)
Clinical Features	- **Hypertension** - **Hypokalemia** (fatigue, muscle cramps) - **Metabolic alkalosis** - **Suppressed renin and aldosterone levels**
Diagnosis	- **History of licorice or offending substance use** - **Low renin and aldosterone** with hyperaldosteronism-like symptoms - **Urinary cortisol-to-cortisone ratio** if SAME is suspected

Category	Details
Treatment	- **Discontinuation of causative agents** (e.g., licorice) - **Potassium-sparing diuretics** (e.g., amiloride) - **Mineralocorticoid receptor antagonists** (e.g., spironolactone) if needed
Key Points for MRCP	- Presents with hyperaldosteronism features without elevated aldosterone. - Licorice and SAME are classic causes. - Distinguish from primary hyperaldosteronism by low aldosterone levels.

Syndrome of Apparent Mineralocorticoid Excess (SAME)

Category	Details
Definition	Rare genetic disorder due to mutations in the **11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2)** enzyme, leading to impaired cortisol metabolism.
Pathophysiology	Deficiency of 11β-HSD2 enzyme leads to **excess cortisol activation of mineralocorticoid receptors**, mimicking aldosterone effects.
Clinical Features	- **Hypertension** (early-onset) - **Hypokalemia** (muscle weakness, fatigue) - **Metabolic alkalosis** - **Low renin and aldosterone**
Complications	- **End-organ damage** due to prolonged hypertension - **Cardiac complications** (left ventricular hypertrophy, arrhythmias)
Diagnosis	- **Low urinary cortisone-to-cortisol ratio** (confirming impaired 11β-HSD2 activity) - **Genetic testing** (for 11β-HSD2 mutations)
Treatment	- **Potassium-sparing diuretics** (e.g., **amiloride**) - **Mineralocorticoid receptor antagonists** (e.g., **spironolactone, eplerenone**) - **Dietary salt restriction**
Key Points for MRCP	- Presents with low renin, low aldosterone, yet hypertension and hypokalemia. - Enzyme deficiency causes cortisol to act like aldosterone.

Phaeochromocytoma

Definition

- Rare, catecholamine-secreting tumour of chromaffin cells, usually located in the adrenal medulla.
- Extra-adrenal tumours (paragangliomas) can occur but are less common.

Pathophysiology

- Tumour secretes excessive catecholamines (epinephrine, norepinephrine, and dopamine), causing episodic or sustained hypertension.
- Catecholamine surges impact the cardiovascular, metabolic, and gastrointestinal systems.

Clinical Features

- **Cardiovascular**: Paroxysmal hypertension, tachycardia, palpitations, orthostatic hypotension.
- **Neurological**: Headaches, sweating, tremors, anxiety, and panic attacks.
- **Gastrointestinal**: Nausea, abdominal pain, weight loss.
- **Others**: Hyperglycemia, heat intolerance.

Complications

- **Cardiovascular**: Hypertensive crises, arrhythmias, myocardial infarction.
- **Metabolic**: Diabetes mellitus, hyperglycemia.
- **Others**: Stroke, renal damage, multi-organ failure during hypertensive crises.

Diagnostic Criteria

1. **Biochemical Testing**: Elevated plasma or urinary metanephrines (normetanephrine and metanephrine).
2. **Imaging**:
   - **CT/MRI**: Preferred for tumour localisation in the adrenal glands.
   - **MIBG Scintigraphy**: Useful for locating extra-adrenal or metastatic tumours.

Treatment

1. **Preoperative Management**:
   - **Alpha-blockers (e.g., phenoxybenzamine)**: Initiated 1-2 weeks prior to surgery to control hypertension.
   - **Beta-blockers**: Added only after adequate alpha blockade to prevent unopposed alpha activity.
   - **Calcium channel blockers**: Alternative if alpha-blockers are poorly tolerated.
2. **Surgical Resection**: Laparoscopic adrenalectomy is the treatment of choice.
3. **Postoperative Care**: Monitor for hypotension, hypoglycemia, and catecholamine withdrawal.

Medications and Doses

Drug	Mode of Action	Dose (Start to Target)	Side Effects	Contraindications
Phenoxybenzamine	Alpha-adrenergic blocker	10 mg BID, titrate as needed	Orthostatic hypotension, fatigue	Severe renal impairment
Propranolol	Beta-blocker	10 mg TID, post-alpha blockade	Bradycardia, fatigue	Asthma, heart block
Nifedipine	Calcium channel blocker	10-20 mg BID	Edema, headache	Severe aortic stenosis

Key Points for MRCP

- **Phaeochromocytoma should be suspected in patients with resistant hypertension and episodic symptoms (headache, sweating, tachycardia).**
- **Preoperative alpha blockade is essential before beta-blockade to avoid hypertensive crises.**
- **Plasma and urinary metanephrines are the most sensitive diagnostic tests.**

Hypoadrenalism

Definition:

Hypoadrenalism, or adrenal insufficiency, is a condition characterized by insufficient production of adrenal hormones, primarily cortisol, and in some cases aldosterone and adrenal androgens.

Types:

1. **Primary Hypoadrenalism (Addison's Disease):** Caused by adrenal gland dysfunction (autoimmune, infectious, or other causes).
2. **Secondary Hypoadrenalism:** Results from insufficient adrenocorticotropic hormone (ACTH) production from the pituitary.
3. **Tertiary Hypoadrenalism:** Occurs due to prolonged suppression of the hypothalamic-pituitary-adrenal (HPA) axis, often due to chronic glucocorticoid therapy.

Pathophysiology:

- Primary adrenal insufficiency leads to a deficiency in cortisol and often aldosterone due to destruction or dysfunction of adrenal glands.
- Secondary adrenal insufficiency arises from a lack of ACTH, leading to decreased cortisol production.

Clinical Features:

- **Common Symptoms:** Fatigue, weakness, weight loss, hypotension, and hyperpigmentation (in primary adrenal insufficiency).
- **Gastrointestinal Symptoms:** Nausea, vomiting, abdominal pain.
- **Psychological Symptoms:** Depression, irritability.

Complications:

- **Adrenal Crisis:** A life-threatening emergency characterized by severe hypotension, shock, and electrolyte imbalances, often triggered by stress, illness, or abrupt withdrawal of glucocorticoids.
- **Electrolyte Imbalance:** Hyponatraemia and hyperkalaemia can occur, particularly in primary hypoadrenalism.

Diagnostic Criteria:

- **Blood Tests:** Low cortisol levels with elevated ACTH in primary adrenal insufficiency; low ACTH in secondary causes.
- **ACTH Stimulation Test:** Evaluates adrenal response to ACTH administration.
- **Imaging:** CT scans may identify adrenal gland abnormalities.

Treatment:

- **Hormone Replacement Therapy:**
  - **Glucocorticoids:** Hydrocortisone is commonly used; doses adjusted according to symptoms and stress levels.
  - **Mineralocorticoids:** Fludrocortisone for primary adrenal insufficiency to manage salt-wasting.
- **Adrenal Crisis Management:** Immediate IV hydrocortisone administration, fluid resuscitation, and electrolyte management.

Comparison of Primary and Secondary Hypoadrenalism

Feature	Primary Hypoadrenalism (Addison's Disease)	Secondary Hypoadrenalism
Aetiology	Adrenal gland dysfunction (autoimmune, infections, tumors, adrenal hemorrhages)	Insufficient ACTH production from the pituitary gland (pituitary tumors, trauma, or suppression due to chronic glucocorticoid use)
Hormone Levels	Low cortisol, high ACTH; low aldosterone in many cases	Low cortisol, low ACTH; normal or high aldosterone levels
Electrolyte Changes	Hyponatraemia and hyperkalaemia due to lack of aldosterone	Typically normal, as aldosterone levels may be preserved
Clinical Features	Fatigue, weight loss, hyperpigmentation, gastrointestinal symptoms, hypotension	Fatigue, weakness, hypotension, but no hyperpigmentation
Diagnosis	Elevated ACTH levels, low cortisol; ACTH stimulation test shows poor response	Low ACTH levels, low cortisol; ACTH stimulation test shows a normal response due to intact adrenal glands
Imaging	CT scan may show adrenal atrophy or other abnormalities	CT scan of the pituitary may reveal tumors or abnormalities
Management	Glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) replacement	Glucocorticoid replacement (hydrocortisone) as needed; address underlying cause (e.g., taper glucocorticoids if due to long-term use)

Feature	Primary Hypoadrenalism (Addison's Disease)	Secondary Hypoadrenalism
Common Causes	Autoimmune adrenalitis, tuberculosis, adrenal metastases	Pituitary adenomas, sudden withdrawal from glucocorticoids, hypothalamic disorders
Symptoms Specificity	More pronounced skin changes (hyperpigmentation), signs of mineralocorticoid deficiency	Lacks hyperpigmentation; symptoms may not be as acute

Corticosteroids Overview

Category	Details
Definition	Corticosteroids are a class of steroid hormones produced in the adrenal cortex, involved in a variety of physiological processes, including inflammation, immune response, and metabolism.
Mechanism of Action	Corticosteroids penetrate cell membranes and bind to glucocorticoid receptors in the cytoplasm, forming a receptor-hormone complex that translocates to the nucleus, where it acts as a transcription factor to modulate gene expression.
Types and Relative Potency	Commonly used corticosteroids: - **Fludrocortisone**: Minimal glucocorticoid, very high mineralocorticoid activity. - **Hydrocortisone**: Glucocorticoid with high mineralocorticoid activity. - **Prednisolone & Betamethasone**: Predominantly glucocorticoid, low mineralocorticoid activity. - **Dexamethasone**: Very high glucocorticoid activity, minimal mineralocorticoid activity. **Steroid Equivalence:** 1 mg prednisolone = 4 mg hydrocortisone 1 mg dexamethasone = 7 mg prednisolone Dexamethasone is approximately 30 times more potent than hydrocortisone.
Therapeutic Uses	Used for conditions such as: - Autoimmune diseases (e.g., rheumatoid arthritis, lupus) - Allergic reactions - Inflammatory diseases (e.g., asthma, inflammatory bowel disease) - Organ transplantation (to prevent rejection)

Category	Details
Side Effects	**Glucocorticoid-related**: - Endocrine: Hyperglycaemia, Cushing's syndrome (moon face, buffalo hump) - Musculoskeletal: Osteoporosis, myopathy - Psychiatric: Mood swings, insomnia, depression - Immunosuppression: Increased infection risk - Gastrointestinal: Peptic ulcers, pancreatitis - Ophthalmic: Cataracts, glaucoma - Growth suppression in children **Mineralocorticoid-related**: - Hypertension, fluid retention
Management of Side Effects	- Monitor bone density and consider bisphosphonates for osteoporosis prevention. - Regular screening for infections, especially during high-dose therapy. - Consider gastroprotective agents (e.g., proton pump inhibitors) to prevent ulcers.
Withdrawal and Dosing	- Gradual tapering is essential to avoid adrenal insufficiency, particularly after prolonged use or high doses (>40 mg prednisolone daily for over one week). - During acute illness, double the dose for short periods.

Cushing's syndrome (Hypercortisolism)

Pathological Definition

- **Cushing's Syndrome**: Hypercortisolism from any cause.
- **Cushing's Disease**: Hypercortisolism caused specifically by an ACTH-secreting pituitary adenoma, accounting for 75% of Cushing's syndrome cases.

Epidemiology

- **Gender**: More common in females (female ratio of 3–15:1).
- **Age**: Primarily affects individuals aged 20–40 years.

Causes

- **Exogenous (Iatrogenic)**:
  - Prolonged glucocorticoid therapy leading to hypercortisolism and bilateral adrenal atrophy. Dexamethasone poses a higher risk compared to shorter-acting agents like prednisone.
- **Endogenous**:
  - **Primary (ACTH-independent)** (5–10%):
    - Autonomous cortisol overproduction from adrenal adenomas, carcinomas, or hyperplasia.
  - **Secondary (ACTH-dependent)**:
    - **Cushing's Disease** (75%): Pituitary adenomas leading to bilateral adrenal hyperplasia.

- **Ectopic ACTH Production** (15%): Associated with malignancies such as small cell lung cancer, causing elevated ACTH levels and bilateral adrenal hyperplasia, often with hypokalemia and weight loss.

- **Pseudo-Cushing's** (Alcohol-induced):
  - Alcoholism may lead to increased CRH secretion, creating a cushingoid appearance but maintaining diurnal cortisol variation.

Clinical Features

- **Skin**: Thin skin, easy bruising, purple abdominal striae, hirsutism, delayed wound healing, facial flushing.
- **Neuropsychological**: Lethargy, depression, sleep disturbances, psychosis.
- **Musculoskeletal**: Osteopenia, osteoporosis, proximal myopathy, pathological fractures.
- **Endocrine/Metabolic**: Insulin resistance, dyslipidemia, fat redistribution (moon face, buffalo hump), decreased libido.
- **Other**: Secondary hypertension, increased infection susceptibility, peptic ulcer disease, cataracts.

Laboratory Findings

- **Common**: Hyperglycemia, hyperlipidemia, hypokalemia, metabolic alkalosis, leukocytosis, low estradiol.

Diagnosis

1. **Screening Tests for Hypercortisolism:**
   - Overnight low-dose dexamethasone suppression test (ODST).
   - 24-hour urinary free cortisol.
   - Late-night salivary cortisol.
2. **Confirm Hypercortisolism**: Follow positive screening with a second test.
3. **ACTH Measurement**:
   - Low ACTH: adrenal source (CT/MRI of adrenal glands).
   - High ACTH: pituitary or ectopic source.
4. **Differentiation Tests:**
   - High-dose dexamethasone suppression test (to distinguish between Cushing's disease and ectopic ACTH).
   - CRH stimulation test (to differentiate Cushing's disease from ectopic ACTH).
   - Inferior Petrosal Sinus Sampling (IPSS) is the gold standard for differentiating between pituitary and ectopic ACTH production.

Treatment

- **Surgical Options**:
  - **Pituitary Adenoma**: Trans-sphenoidal hypophysectomy.
  - **Adrenocortical Tumors**: Laparoscopic/open adrenalectomy.
  - Ectopic ACTH tumors: Resection of the source.
- **Medical Management**:
  - Unfit for surgery: Ketoconazole or Mitotane for symptom management.
  - **Pre-surgical**: Metyrapone to improve metabolic parameters.

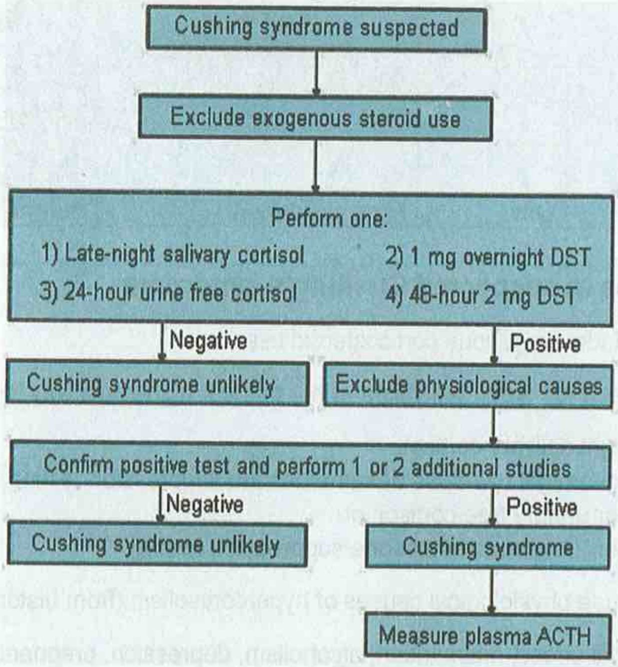
Summary Table of Cushing's Causes

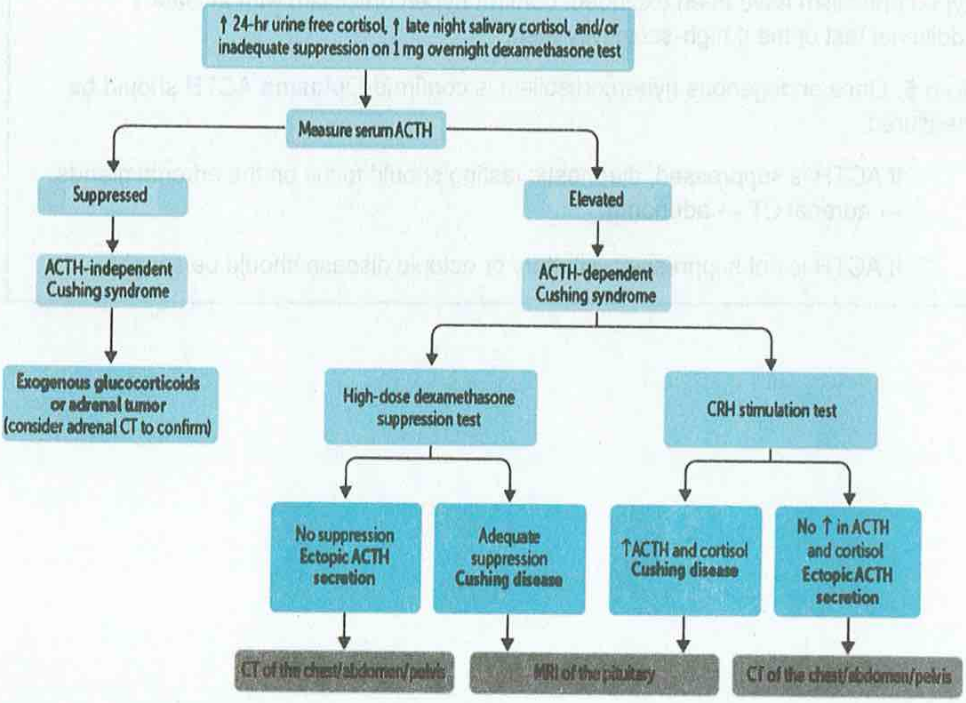
Source	ACTH Level	High-dose Dexamethasone	Specific Test
Pituitary Tumor	High	Suppression	MRI, Petrosal vein sampling
Ectopic ACTH Production	High	No suppression	CT scan of chest/abdomen
Adrenal Adenoma	Low	No suppression	Adrenal scan

Diagnostic steps in suspected Cushing's syndrome

- **Step 1** : Exclude exogenous corticosteroid use
- **Step 2** : Screen for hypercortisolism with 1 of the 4 high-sensitivity tests
  1) late-night salivary cortisol;
  2) 1 mg overnight low-dose dexamethasone suppression testing,
  3) 24-hour urinary free cortisol; or
  4) 48-hour 2 mg dexamethasone suppression testing.
- **Step 3:** Exclude physiological causes of hypercortisolism (from history)
  - ⇨ physical stress, malnutrition, alcoholism, depression, pregnancy, class III obesity (BMI 40 or above) or metabolic syndrome.
- **Step 4:** If an initial screening test is positive , and physiological causes of hypercortisolism have been excluded: confirm hypercortisolism with at least 1 additional test of the 4 high-sensitivity tests.
- **Step 5:** Once endogenous hypercortisolism is confirmed, **plasma ACTH** should be measured.
  - ⇨ If ACTH is suppressed, diagnostic testing should focus on the adrenal glands. → adrenal CT → adenoma.
  - ⇨ If ACTH is not suppressed, pituitary or ectopic disease should be sought.

Algorithm for the diagnosis of Cushing syndrome





Diabetology

Metabolic syndrome

Pathophysiology

- **Insulin Resistance**: Characterized by adipose tissue dysfunction; increased visceral fat releases inflammatory cytokines (e.g., TNF-α, IL-6), impairing insulin sensitivity.

Diagnostic criteria

- **WHO Criteria (1999)**:
  - Presence of insulin resistance (Type 2 diabetes mellitus, impaired glucose tolerance, or impaired fasting glucose) plus **two** of the following:
    1. Blood pressure: > 140/90 mmHg
    2. Dyslipidaemia:
       - Triglycerides: > 1.695 mmol/L
       - HDL-C: < 0.9 mmol/L (male), < 1.0 mmol/L (female)
    3. Central obesity:
       - Waist-to-hip ratio: > 0.90 (male), > 0.85 (female)
       - BMI: > 30 kg/m²
    4. Microalbuminuria:
       - Urinary albumin excretion ratio > 20 mg/min or
       - Albumin: creatinine ratio > 30 mg/g

Risk Factors

- **Non-modifiable**:
  - Age, ethnicity (higher risk in South Asians), family history.
- **Modifiable**:
  - Sedentary lifestyle, poor diet (high in refined sugars and fats), obesity, smoking.

Complications

- **Cardiovascular Diseases**: Increased risk of coronary artery disease, stroke, and peripheral vascular disease.
- **Type 2 Diabetes Mellitus**: Higher risk of progression from insulin resistance to Type 2 DM.
- **Non-alcoholic Fatty Liver Disease (NAFLD)**.

Management

1. **Lifestyle Modification (First-line)**:
   - **Weight Loss**: Aim for a 5-10% reduction in body weight.
   - **Diet**: Emphasize vegetables, whole grains, lean proteins, and healthy fats.
   - **Exercise**: At least 150 minutes of moderate aerobic activity weekly.
   - **Behavioral Changes**: Smoking cessation and limiting alcohol intake.
   - **Mechanism**: Long-term exercise enhances GLUT4 expression, potentially reducing hyperglycemia.
2. **Pharmacological Management (if lifestyle measures are insufficient)**:
   - **Dyslipidaemia**: Statins.
   - **Hypertension**: ACE inhibitors or ARBs.
   - **Impaired Glucose Tolerance or Type 2 DM**: Metformin.
   - **Weight Management**: Orlistat reduces diabetes risk by 38% more than diet alone in obese patients.
3. **Surgical Options**:
   - Consider bariatric surgery for patients with a BMI ≥ 35 kg/m² and coexisting metabolic syndrome when conservative measures fail.

Pre-diabetes or impaired glucose regulation (IGR)

Definition:

- **Pre-diabetes** (also known as **Impaired Glucose Regulation, IGR**) is a metabolic condition characterized by blood glucose levels that are higher than normal but not high enough to be classified as diabetes. It includes two specific categories: **Impaired Fasting Glucose (IFG)**, where fasting blood glucose is 100-125 mg/dL (5.6-6.9 mmol/L), and **Impaired Glucose Tolerance (IGT)**, where 2-hour plasma glucose during an oral glucose tolerance test (OGTT) is 140-199 mg/dL (7.8-11.0 mmol/L). Individuals with pre-diabetes are at increased risk of developing Type 2 diabetes and cardiovascular diseases.

Diagnosis of prediabetes

	normal	Prediabetes	Diabetes mellitus
Fasting glucose	≤ 6 mmol/l	≥ 6.1 – 6.9 mmol/l impaired fasting glucose (IFG)	≥ 7 mmol/l
2h glucose during an OGTT	< 7.8 mmol/l	7.8 -n 11 mmol/l Impaired glucose tolerance (IGT)	≥ 11.1 mmol/l
HA1c	< 42 mmol/mol < 6%	42 – 47 mmol/mol (6.0 – 6.4%)	≥ 6.5%

Comparison between Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT)

Aspect	Impaired Fasting Glucose (IFG)	Impaired Glucose Tolerance (IGT)
Definition	Elevated fasting blood glucose, but not high enough for diabetes.	Elevated blood glucose post-oral glucose load, but not high enough for diabetes.
Diagnostic Criteria (WHO)	Fasting plasma glucose: **6.1 - 6.9 mmol/L**	2-hour plasma glucose after a 75g oral glucose tolerance test (OGTT): **7.8 - 11.0 mmol/L**
Mechanism	Primarily reflects **hepatic** insulin resistance.	Reflects **peripheral (muscle)** insulin resistance.
Risk of Progression to T2DM	**High risk**, though less than IGT.	**Higher risk** compared to IFG.
Risk of Cardiovascular Disease	Moderate risk compared to normoglycemia.	Higher risk compared to IFG and normoglycemia.
Prevalence	**More commonly detected** in clinical practice due to routine fasting glucose measurements.	**Less commonly detected** as OGTT is less frequently used.
Screening Recommendation	Routine screening with fasting glucose in at-risk populations (e.g., obesity, hypertension).	OGTT in high-risk populations or if fasting glucose is inconclusive.

Risk of Drugs Associated with Impaired Glucose Tolerance and Type 2 Diabetes

Drug Class	Risk Mechanism	Increased risk of T2DM (Higher to Lower)
Atypical Antipsychotics (e.g., Olanzapine, Clozapine)	Weight gain, insulin resistance, impaired glucose metabolism	30-40%
Protease Inhibitors (e.g., Ritonavir)	Insulin resistance, impaired beta-cell function	20-30%
Glucocorticoids	Increased hepatic gluconeogenesis, insulin resistance	20% (dose-dependent)
Calcineurin Inhibitors (e.g., Tacrolimus, Cyclosporine)	Impaired insulin secretion	15-20%
Thiazide Diuretics	Hypokalemia, reduced insulin sensitivity	10-15%
Beta-Blockers	Reduced insulin sensitivity, impaired beta-cell function	10-15%
Niacin (High Doses)	Insulin resistance	5-10%
Statins (e.g., Atorvastatin)	Impaired insulin sensitivity	5-10% (dose-dependent)
SSRIs (e.g., Fluoxetine)	Weight gain, metabolic changes	Mild association with impaired glucose tolerance

Complication

- Progression to type 2 diabetes mellitus (T2DM). **The risk of developing type 2 diabetes in patients with (IGT) → 60% over 6 years**
- ↑ Risk of macrovascular disease (e.g. coronary artery disease). There is no risk of microvascular complications of diabetes, such as retinopathy and nephropathy.

Management

- **1st line: Intensive lifestyle change**: weight loss (of 5% of initial body weight), increased exercise, change in diet → reduce progression from prediabetes to frank type 2 diabetes by approximately 50%.
- **2nd line:** if still progressing towards type 2 diabetes, despite an intensive lifestyle-change programme → metformin.

Diabetes mellitus: Type 1 overview

Definition

- **Type 1 Diabetes Mellitus (T1DM)** is an autoimmune disorder characterized by the destruction of pancreatic beta cells, leading to absolute insulin deficiency. This results in elevated blood glucose levels (hyperglycemia) and requires lifelong insulin therapy for management.

Pathophysiology

- **Autoimmune Destruction**: The immune system attacks and destroys insulin-producing beta cells in the pancreas, primarily mediated by T lymphocytes.
- **Insulin Deficiency**: The complete lack of insulin leads to an inability to regulate blood glucose effectively, resulting in increased hepatic glucose production and impaired glucose uptake by peripheral tissues.
- **Ketoacidosis**: Due to insulin deficiency, the body shifts to fat metabolism, producing ketones, which can lead to diabetic ketoacidosis (DKA), a life-threatening condition.

Risk Factors

- **Genetic Factors**:
  - Family history of autoimmune diseases, particularly T1DM.
  - Certain genetic markers (e.g., HLA-DR3 and HLA-DR4).
- **Environmental Triggers**:
  - Viral infections (e.g., Coxsackie virus).
  - Early exposure to cow's milk proteins.
  - Other autoimmune conditions (e.g., thyroid disease, celiac disease).

Clinical Features

- **Common Symptoms**:
  - Polyuria (increased urination)
  - Polydipsia (increased thirst)
  - Polyphagia (increased hunger)
  - Weight loss despite normal or increased appetite.
  - Fatigue and weakness.
- **Acute Presentation**:
  - May present acutely with diabetic ketoacidosis (DKA), characterized by nausea, vomiting, abdominal pain, altered mental status, and rapid breathing.

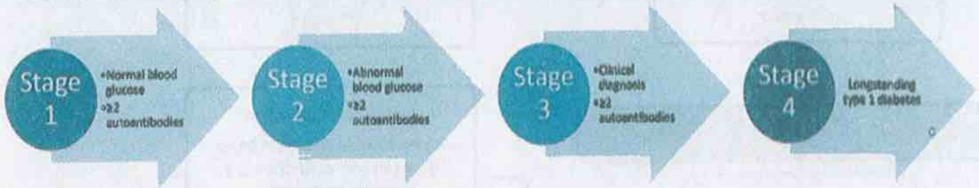
Diagnostic Criteria

Test	Threshold for Diagnosis
Fasting Plasma Glucose	≥7.0 mmol/L (126 mg/dL)
2-hour Post-OGTT	≥11.1 mmol/L (200 mg/dL)
Random Plasma Glucose	≥11.1 mmol/L (200 mg/dL) with classic symptoms
HbA1c	≥48 mmol/mol (≥6.5%)

- Diagnosis requires confirmation with a repeat test unless classic hyperglycemic symptoms are present.

Stages of type 1 DM

Stage	Description	Key Features
Stage 1	**Autoimmunity without Dysglycemia**	- Presence of ≥1 of **islet autoantibodies** (1GAD, ICA, ZnT8, or IAA). - Normal blood glucose levels. - No symptoms. - often identified through screening (e.g., in relatives of T1DM patients).
Stage 2	**Autoimmunity with Dysglycemia (Pre-symptomatic)**	- Islet autoantibodies (≥1). - **Dysglycemia** (impaired fasting glucose or glucose tolerance). - No symptoms.
Stage 3	**Clinical T1DM (Symptomatic)**	- Onset of **hyperglycemia.** - Typical symptoms: polyuria, polydipsia, weight loss. - Often diagnosed during DKA
Stage 4	**Long-Standing T1DM (Chronic Disease)**	- Progressive insulin dependence. - Risk of complications (e.g., microvascular and macrovascular complications).



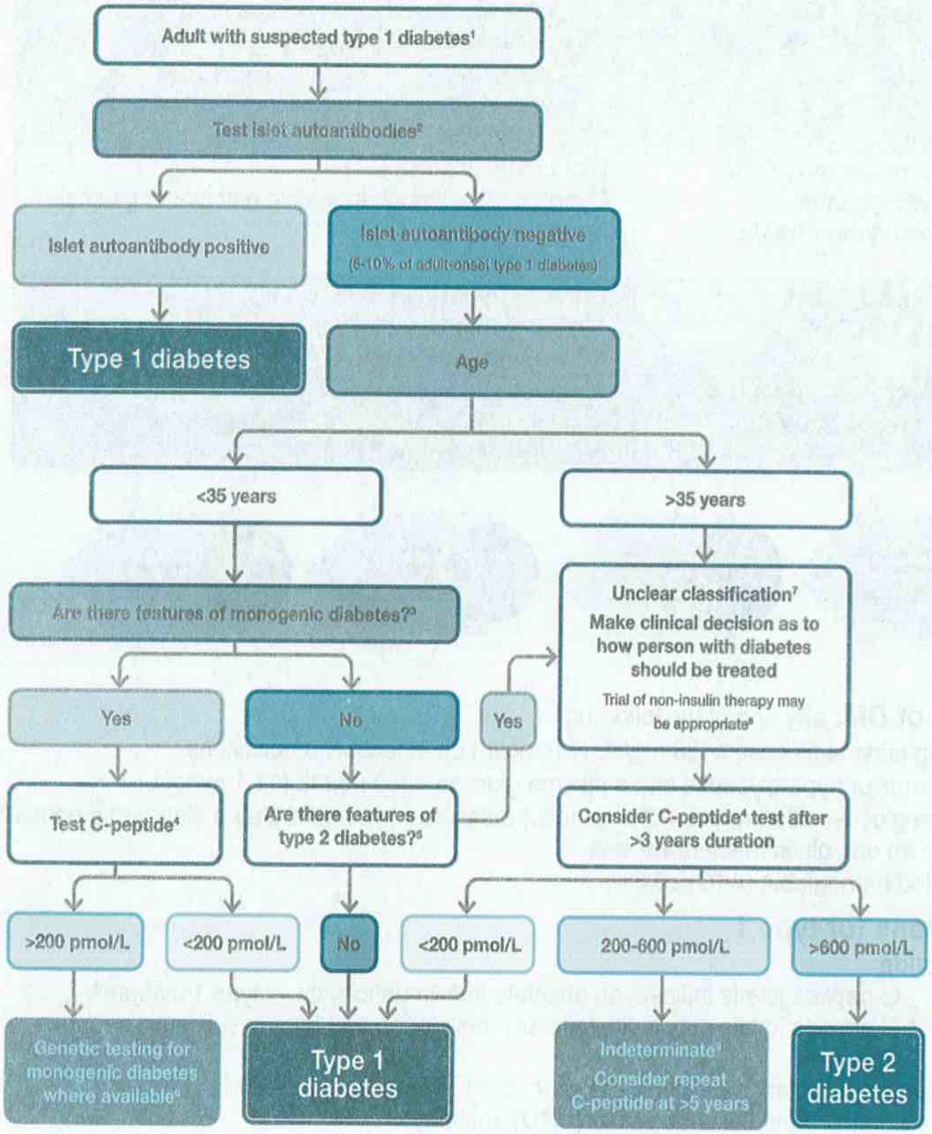
Diagnosis of DM: any one of the following

- Fasting plasma glucose ≥126 mg/dL (7 mmol/L) on at least two occasions
- Symptoms of hyperglycemia and a plasma glucose ≥200 mg/dL (11.1 mmol/L)
- Plasma glucose ≥200 mg/dL (11.1 mmol/L) measured two hours after a standard glucose load in an oral glucose tolerance test
- Glycated hemoglobin (A1C) ≥6.5%.

Investigations for type 1

- **C-peptide**
  - ⇨ ↓ C-peptide levels indicate an absolute insulin deficiency → type 1 diabetes
  - ⇨ ↑ C-peptide levels may indicate insulin resistance and hyperinsulinemia → type 2diabetes
- **Antibodies** detected in patients who later go on to develop type 1 DM:
  - ⇨ Glutamic Acid Decarboxylase **(GAD)** antibody
    - **found in 70-90% of type1 diabetics.**
    - 10 fold increases the risk of developing IDDM.
    - 10% of adults who have been classified as having type 2 diabetes may have (ICA) or (GAD) antibodies, indicating autoimmune destruction of beta cells.
  - ⇨ Islet Cell Antibodies (ICA): **found in up to 60 - 80% of patients with type 1 diabetes**

Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations



[1]**Features suggest T1DM:** younger age at diagnosis (<35 years), with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >20 mmol/L (>360 mg/dL) at presentation.
[2]**GAD should be tested first** and, if negative, should be followed by islet tyrosine phosphatase 2 (IA2) and/or zinc transporter 8 (ZNT8). In age <35 years without features of T2DM or monogenic DM, a negative result does not exclude T1DM (since 5–10% of T1DM do not have antibodies).
[3]**Monogenic diabetes is suggested by the presence of one or more of the following features:** HbA_{1c} <58 mmol/mol (7.5%) at diagnosis, one parent with diabetes, features of specific monogenic cause

(e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model probability >5% (www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator).

[4]**A C-peptide test is only indicated in people receiving insulin treatment.** A random sample (with concurrent glucose) within 5 h of eating can replace a formal C-peptide stimulation test in the context of classification. If the result is ≥600 pmol/L, the circumstances of testing do not matter. If the result is <600 pmol/L and the concurrent glucose is <4 mmol/L (<72 mg/dL) or the person may have been fasting, consider repeating the test. Results showing very low levels (<80 pmol/L) do not need to be repeated. Where a person is insulin-treated, C-peptide must be measured prior to insulin discontinuation to exclude severe insulin deficiency. Do not test C-peptide within 2 weeks of a hyperglycemic emergency.

[5]**Features of type 2 diabetes include** increased BMI (≥25 kg/m^2), absence of weight loss, absence of ketoacidosis, and less marked hyperglycemia.

[6]**If genetic testing does not confirm monogenic diabetes,** the classification is unclear and a clinical decision should be made about treatment.

[7]**Type 2 diabetes should be strongly considered in older individuals.** In some cases, investigation for pancreatic or other types of diabetes may be appropriate.

[8]A person with possible type 1 diabetes who is not treated with insulin will require careful monitoring and education so that insulin can be rapidly initiated in the event of glycemic deterioration.

[9]**C-peptide values 200–600 pmol/L are usually consistent with type 1 diabetes or maturity-onset diabetes of the young (MODY)** but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low BMI or after long duration.

Complications

- **Acute Complications**:
  - **Diabetic Ketoacidosis (DKA)**: A serious condition due to severe insulin deficiency, characterized by metabolic acidosis and ketonemia.
- **Chronic Complications**:
  - **Microvascular**:
    - **Retinopathy**: Leading cause of blindness in adults.
    - **Nephropathy**: Progressive kidney disease can lead to end-stage renal disease (ESRD).
    - **Neuropathy**: Peripheral neuropathy (pain, numbness) and autonomic neuropathy (e.g., gastroparesis, erectile dysfunction).
  - **Macrovascular**:
    - **Cardiovascular Disease**: Increased risk of coronary artery disease, myocardial infarction, and stroke.
    - **Peripheral Arterial Disease**: Increased risk of limb ischemia and amputations.
- **Psychosocial Issues**:
  - Increased risk of anxiety, depression, and diabetes-related distress.

Type 1 Diabetes Mellitus: Step-by-Step Management

1. Initial Management and Education

- **Patient Education**:
  - Intensive diabetes education on insulin use, blood glucose monitoring, hypoglycemia management, and carbohydrate counting.
- **Self-Monitoring of Blood Glucose (SMBG)**:
  - Minimum of 4 times daily (before meals and at bedtime); more frequent if adjusting insulin or during physical activities.

2. Insulin Therapy Initiation

- **Basal-Bolus Regimen**:
  - **Basal Insulin**: Once-daily dose of long-acting insulin (e.g., insulin glargine or detemir).
  - **Bolus Insulin**: Rapid-acting insulin (e.g., insulin aspart or lispro) before meals, with dose adjustments based on carbohydrate intake and pre-meal glucose.
- **Starting Dosage**:
  - **Total Daily Dose**: 0.4-0.6 units/kg body weight.
  - Split into ~50% basal and ~50% bolus insulin.

3. Continuous Glucose Monitoring (CGM) and Advanced Insulin Delivery

- **CGM**: Recommended for all Type 1 patients if available, to provide real-time glucose trends and reduce hypoglycemia risk.
- **Insulin Pump Therapy**: Considered in patients struggling with glycemic control on injections or who desire more flexible insulin delivery.

4. Ongoing Adjustments and Monitoring

- **HbA1c Monitoring**: Every 3 months to assess long-term control, aiming for target <7.0% (53 mmol/mol) without excessive hypoglycemia.
- **Daily Adjustments**:
  - **Correction Doses**: Use rapid-acting insulin to correct high blood sugar, based on insulin sensitivity factor.
  - **Carbohydrate Counting and Insulin-to-Carb Ratios**: Adjust bolus insulin based on carbohydrate intake at meals.
- **Regular Assessment of Insulin Sensitivity**:
  - Adjust basal and bolus doses as needed based on SMBG/CGM data and lifestyle changes (e.g., exercise, illness).

5. Management of Hypoglycemia

- **Prevention**:
  - Frequent glucose monitoring and using CGM to predict low blood sugars.
  - Adjust insulin during exercise and for variations in daily routine.
- **Treatment**:
  - Immediate consumption of 15-20g of fast-acting carbohydrates, with follow-up monitoring and additional carbs if needed.

6. Monitoring and Managing Complications

- **Diabetic Ketoacidosis (DKA)**: Educate on early signs (e.g., nausea, abdominal pain, fruity breath) and seek prompt treatment.
- **Screening for Complications**:
  - Annual eye exams, kidney function tests, lipid profile, and foot exams.
- **Psychosocial Support**: Routine assessment of mental health, especially in young adults and adolescents, to support adherence and reduce diabetes-related distress.

Summary Table of Insulin Therapy in Type 1 Diabetes

Step	Details
Basal Insulin	Long-acting insulin once daily (e.g., glargine or detemir)
Bolus Insulin	Rapid-acting insulin before meals; dose adjusted by carb counting and glucose level
Total Daily Dose	Initial dose of 0.4-0.6 units/kg, divided into ~50% basal and ~50% bolus
Insulin Pump (optional)	For patients desiring flexible insulin delivery or with unstable glucose control
Continuous Monitoring	CGM for real-time glucose trends, especially to manage hypoglycemia and fine-tune insulin
Target HbA1c	<7.0% (53 mmol/mol) without hypoglycemia
Hypoglycemia Management	15-20g fast-acting carbs, re-check glucose in 15 minutes; prevent with CGM and careful dosing

Glycemic and Clinical Targets in Type 1 Diabetes Management

Parameter	Target
HbA1c	<7.0% (53 mmol/mol) for most adults; <7.5% for children and adolescents (individualized per patient risk)
Pre-meal (fasting) glucose	4.4-7.2 mmol/L (80-130 mg/dL)
Postprandial glucose (1-2 hours after meals)	<10.0 mmol/L (<180 mg/dL)
Time in Range (TIR)	≥70% of readings within 3.9-10 mmol/L (70-180 mg/dL)
Blood Pressure	<140/90 mmHg; lower targets (e.g., <130/80 mmHg) may be appropriate for some patients
LDL Cholesterol	<2.6 mmol/L (<100 mg/dL) for most adults; <1.8 mmol/L (<70 mg/dL) in patients with high cardiovascular risk
Body Mass Index (BMI)	18.5-24.9 kg/m²
Hypoglycemia	Minimize episodes of blood glucose <3.9 mmol/L (<70 mg/dL); avoid severe hypoglycemia

Diabetes mellitus: Type 2 overview

Definition

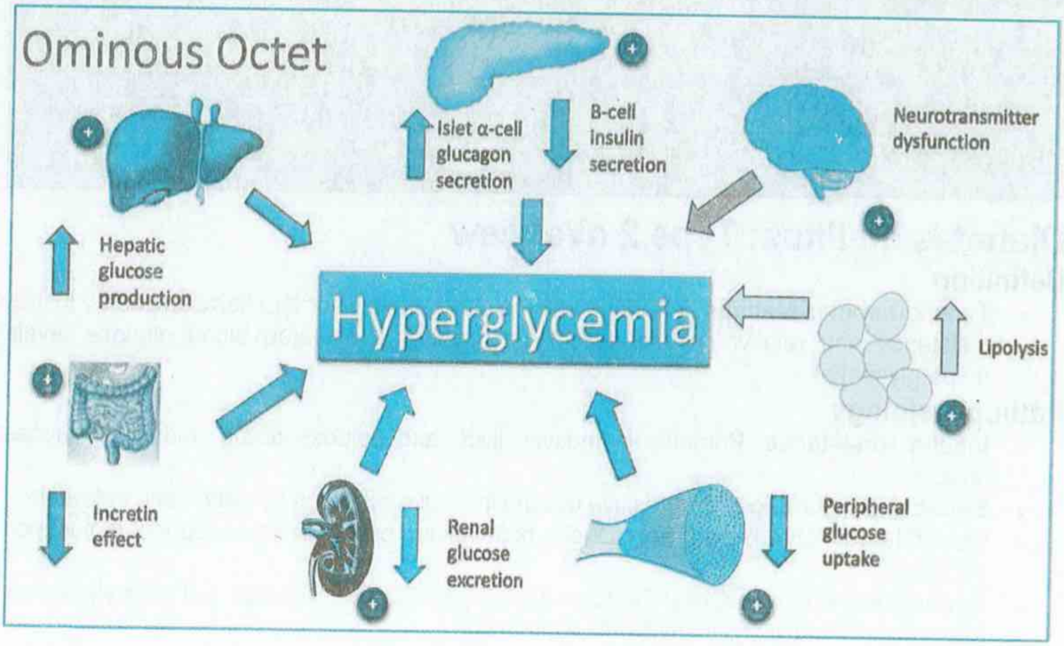
- **Type 2 Diabetes Mellitus (T2DM)** is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency, leading to elevated blood glucose levels (hyperglycemia).

Pathophysiology

- **Insulin Resistance**: Primarily in muscle, liver, and adipose tissue, reducing glucose uptake.
- **Beta-cell Dysfunction**: Progressive decline in insulin secretion by pancreatic beta-cells.
- **Liver Glucose Overproduction**: Due to both insulin resistance and unopposed glucagon secretion.
- **Genetic and Environmental Factors**: Strong genetic predisposition, with lifestyle factors (diet, physical inactivity) significantly contributing.
- The **Ominous Octet**, describes the eight pathophysiological abnormalities that contribute to the development and progression of T2DM.

Components of the Ominous Octet

Defect	Affected Organ/System	Pathophysiology
1. Beta-Cell Dysfunction	Pancreas	- Decreased insulin secretion due to beta-cell failure.
2. Insulin Resistance	Skeletal Muscle	- Impaired glucose uptake, contributing to hyperglycemia.
3. Increased Hepatic Glucose Production	Liver	- Excess gluconeogenesis and glycogenolysis, especially in fasting state.
4. Lipotoxicity	Adipose Tissue	- Increased free fatty acid (FFA) release exacerbates insulin resistance.
5. Decreased Incretin Effect	Gut	- Reduced secretion and/or action of GLP-1 and GIP, impairing insulin response.
6. Hyperglucagonemia	Pancreas (Alpha Cells)	- Excess glucagon secretion increases hepatic glucose production.
7. Increased Renal Glucose Reabsorption	Kidney	- Elevated SGLT2-mediated glucose reabsorption in proximal tubules.
8. Neurotransmitter Dysfunction	Brain	- Impaired hypothalamic regulation of appetite and energy balance; contributes to insulin resistance. - Decrease in the morning dopamine surge → decrease in insulin sensitivity. - increase in sympathetic tone.



Risk Factors

- **Modifiable**:
    - Obesity (especially central obesity)
    - Physical inactivity
    - Unhealthy diet (high-calorie, low-nutrient foods)
    - Smoking
- **Non-Modifiable**:
    - Family history of diabetes
    - Age >45 years
    - Ethnicity (higher risk in South Asian, African, and Hispanic populations)
    - History of gestational diabetes or polycystic ovary syndrome (PCOS)

Clinical Features

- Often asymptomatic in early stages.
- **Common Symptoms**:
    - Polyuria, polydipsia, and polyphagia.
    - Fatigue, blurred vision, slow wound healing.
    - Recurrent infections (e.g., urinary or skin infections).
- **Late Symptoms** (due to complications):
    - Numbness or tingling in hands/feet (neuropathy)
    - Vision changes (retinopathy)
    - Chest pain, shortness of breath (cardiovascular disease)

Diagnostic Criteria

Test	Threshold for Diabetes
Fasting Plasma Glucose	≥7.0 mmol/L (126 mg/dL)
2-hour Post-OGTT	≥11.1 mmol/L (200 mg/dL)
Random Plasma Glucose	≥11.1 mmol/L (200 mg/dL) with classic symptoms
HbA1c	≥48 mmol/mol (≥6.5%)

- Diagnosis requires **two abnormal test results** from the same sample or separate days unless symptoms are present.

Complications

- **Microvascular**:
    - **Retinopathy**: Leading cause of blindness in adults.
    - **Nephropathy**: May progress to chronic kidney disease (CKD) and end-stage renal disease (ESRD).
    - **Neuropathy**: Peripheral neuropathy (pain, numbness) and autonomic neuropathy (gastroparesis, erectile dysfunction).
- **Macrovascular**:
    - **Cardiovascular Disease**: Increased risk of coronary artery disease, myocardial infarction.
    - **Cerebrovascular Disease**: Higher risk of stroke.
    - **Peripheral Arterial Disease**: Increased risk of limb ischemia and amputation.
- **Other Complications**:
    - Increased susceptibility to infections.
    - Nonalcoholic fatty liver disease (NAFLD).

Glycosylated haemoglobin (HbA1c)

Comprehensive HbA1c Overview

Parameter	Description
Definition	HbA1c reflects the percentage of hemoglobin molecules bound to glucose, indicating average blood glucose over 2-3 months.
Diagnostic Ranges	- **Normal**: <42 mmol/mol (<6.0%) - **Pre-diabetes**: 42-47 mmol/mol (6.0-6.4%) - **Diabetes**: ≥48 mmol/mol (≥6.5%)
Glycemic Targets	- **Lifestyle or Metformin Only**: 48 mmol/mol (6.5%) - **Therapies with Hypoglycemia Risk**: 53 mmol/mol (7.0%)
Testing Frequency	- **Every 6 months**: Stable glycemic control - **Every 3 months**: Recently adjusted therapy or suboptimal control
Causes of Falsely High HbA1c	- Hemoglobinopathies (e.g., sickle cell trait) - Iron deficiency anemia - Chronic kidney disease (CKD) - Vitamin B12 supplementation (long-standing deficiency)
Causes of Falsely Low HbA1c	- Hemoglobinopathies (e.g., thalassemia) - Hemolytic anemia - Advanced CKD (shortened RBC lifespan) - Recent blood transfusion - Erythropoietin therapy - Pregnancy (increased RBC turnover)
Alternative Markers	- **Fructosamine**: Reflects 2-3 weeks of glucose control - **Glycated Albumin**: Reflects 2-4 weeks of glucose control - **1,5-Anhydroglucitol (1,5-AG)**: Indicates postprandial glucose spikes - **Continuous Glucose Monitoring (CGM)**: Provides real-time glucose trends - **Fasting Plasma Glucose (FPG)**: Measures current glucose levels - **Oral Glucose Tolerance Test (OGTT)**: Measures glucose response over time

Type 2 Diabetes mellitus: Step-by-Step Management

1. Initial Assessment and Lifestyle Modification

- **Assess**:
  - HbA1c level to gauge baseline control and treatment targets.
  - Body weight, blood pressure, lipid profile, and comorbidities.
- **Lifestyle Intervention**:
  - **Diet**: Individualized, focusing on calorie restriction and balanced macronutrients.
  - **Exercise**: 150 minutes of moderate-intensity exercise per week plus resistance training.
  - **Weight Loss**: Aim for 5-10% weight loss if BMI >25 kg/m².

2. Monotherapy Initiation (HbA1c <7.5%)

- **First-line Therapy**:
  - **Metformin**: Start with 500 mg once or twice daily, titrate as tolerated up to 2000 mg daily.
  - **Alternative for Metformin intolerance**: SGLT2 inhibitor or GLP-1 receptor agonist if cardiovascular or renal risk factors are present.
- **Monitor**: Reassess HbA1c in 3 months to determine efficacy.

3. Dual Therapy (HbA1c ≥7.5% Despite Monotherapy)

- **Add-on Agents** (selected based on patient profile):
  - **SGLT2 Inhibitors**: Preferred for patients with heart failure or chronic kidney disease.
  - **GLP-1 Receptor Agonists**: Considered if weight loss is a goal and cardiovascular risk is elevated.
  - **DPP-4 Inhibitors** or **Thiazolidinediones (TZDs)**: Options when SGLT2 inhibitors or GLP-1 agonists are contraindicated.
- **Note**: Avoid combining GLP-1 and DPP-4 inhibitors due to overlapping mechanisms.

4. Triple Therapy (HbA1c >8% on Dual Therapy)

- **Third Agent Addition**:
  - Use an agent with a complementary mechanism, e.g., adding insulin or a TZD.
  - Consider adding **basal insulin** if HbA1c remains elevated, starting with 10 units or 0.1-0.2 units/kg/day, titrating based on fasting glucose levels.
- **Adjust Therapy**: Optimize doses for all three agents, monitoring for hypoglycemia.

5. Intensified Therapy (HbA1c >9% or Acute Symptomatic Hyperglycemia)

- **Combination Injectable Therapy**:
  - **Basal-Bolus Insulin Regimen**: Consider basal insulin plus pre-meal rapid-acting insulin.
  - **GLP-1 Agonist with Basal Insulin**: If weight loss is desired and there is a need to minimize hypoglycemia.
- **Monitoring and Titration**: Frequent monitoring of blood glucose; adjust doses to achieve target control.

6. Long-term Monitoring and Follow-up

- **HbA1c Monitoring**: Every 3 months until stable, then every 6 months.
- **Comorbidity Management**: Regular cardiovascular, renal, and eye assessments.
- **Lifestyle Reassessment**: Continuously support dietary and exercise goals.
- **Patient Education**: Focus on self-monitoring, recognition of hypoglycemia, and adherence to lifestyle and medication.

7. Special Considerations and Additional Therapeutic Goals

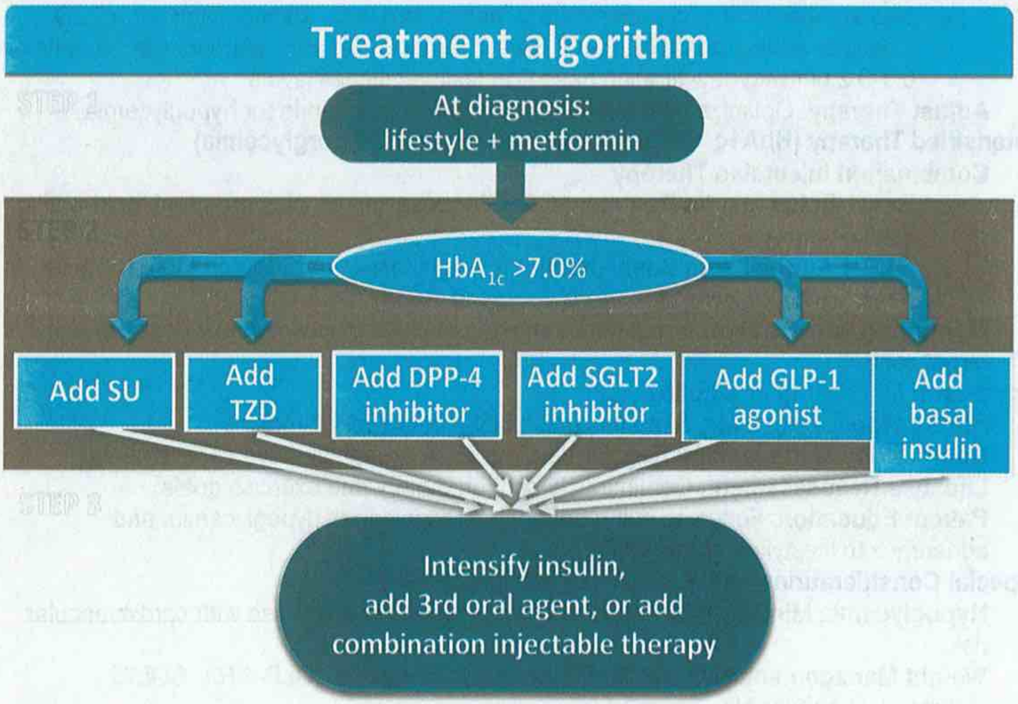
- **Hypoglycemia Minimization**: Especially for older adults and those with cardiovascular risk.
- **Weight Management**: Use agents with weight loss benefits (GLP-1 RA, SGLT2 inhibitors) when feasible.
- **Cardiorenal Protection**: Prioritize SGLT2 inhibitors or GLP-1 agonists in patients with cardiovascular or renal disease.

Summary Table of Therapy Escalation

HbA1c Level	Primary Intervention	Drug Options
<7.5%	Lifestyle + Metformin	Metformin or GLP-1 RA/SGLT2 if intolerant
≥7.5% on Monotherapy	Add Dual Therapy	SGLT2 inhibitor, GLP-1 RA, DPP-4 inhibitor, or TZD based on risks
≥8% on Dual Therapy	Triple Therapy	Add insulin or third oral agent; titrate to achieve targets
>9% or symptomatic	Combination Injectable Therapy	Basal-bolus insulin or basal + GLP-1 RA

HbA1c targets

Management Strategy	HbA1c Target
Lifestyle intervention alone or lifestyle + metformin	48 mmol/mol (6.5%)
Therapy including any drug that may cause hypoglycemia (e.g., sulfonylureas)	53 mmol/mol (7.0%)



Step 2 consideration

	Metformin Plus...					
	SU	TZD	DPP-4	GLP-1 RA	SGLT2-I	Insulin
↓ HbA_{1c}	↓↓	↓	↓	↓↓	↓	↓↓
Hypo-glycemia	High	Low	Low	Low	Low	High
Weight	Gain	Gain	Neutral	Loss	Loss	Gain
Side Effects	Hypo-glycemia, weight gain	Edema, CHF, Fx, weight gain	Rare	GI	Candida	Hypo-glycemia, weight gain
Cost	Low	Low	High	High	High	High

Biguanides (metformin)

Mode of action	▪ Inhibits intestinal glucose absorption ▪ Inhibits mitochondrial glycerophosphate dehydrogenase → ↓ **hepatic gluconeogenesis** ▪ Increases peripheral insulin sensitivity (↓ **Insulin resistance**) → ↑**Peripheral glucose uptake**
Advantages	▪ Glycemic efficacy: lowers HbA1c by 1.2–2% over 3 months ▪ **Weight loss** ▪ **No risk of hypoglycemia** ▪ **Reduce macrovascular complications** and death (superior to sulphonylureas and insulin in terms of macrovascular risk, e.g. myocardial infarction).
Adverse effects	▪ Gastrointestinal upsets (nausea, high dose (> 2 gm daily) ↓ **bile salts reabsorption from the ileum → chronic diarrhoea)**, intolerable in 20%. Reduced by gradual dose titration every week and using modified release preparations. ▪ **Vitamin B_{12} deficiency** (cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia). ▪ **Lactic acidosis** (rare) occurs in patients with severe liver disease, renal failure, **alcohol** intake, recent myocardial infarction (stop for 6 weeks after MI), and sepsis.
Contraindications	▪ **Chronic kidney disease stage 4:** if the creatinine is > 150 mmol/l or **eGFR < 30 ml/min**) (if the creatinine is > 130 mmol/l or **eGFR < 45** ml/min → reduce those and monitor renal function every three months) ▪ **Alcohol abuse is a relative contraindication → ↑risk of lactic acidosis** ▪ **Heart failure (NYHA III and IV), respiratory failure, shock, sepsis**

Sulphonylureas

Mode of action	▪ Block ATP-sensitive potassium channels (KATP) of the pancreatic β cells → ↑**Insulin secretion**
Agents	▪ **Glibenclamide:** long half-life with a high risk of hypoglycaemia (should be avoided in the elderly). Renally excreted: renal impairment →↑ risk of hypoglycaemia ▪ **Gliclazide:** intermediate half-life of around 11 hours. causes less hypoglycemia than other sulfonylureas. metabolised within the liver, so can be used safely In CKD stages 1, 2, and 3 (eGFR > 30 mL/min). In patients with severe CKD, a reduced dose can be used ▪ **Glipizide:** the best choice of sulfonylureas in a patient with renal impairment (no need for dose adjustment) as it is metabolized by the liver. ▪ **Chlorpropamide** has a higher side effect profile and may produce a syndrome of inappropriate anti-diuretic hormone (ADH) secretion.
Advantages	▪ provides **micro**vascular benefits, but **NO benefit was demonstrated for macrovascular outcomes** (cardiovascular disease), in contrast to metformin.
Adverse effects	▪ **Hypoglycemia:** the risk is increased with age over 65, renal failure, and long-acting Sulphonylureas such as chlorpropamide and glyburide (glibenclamide). ▪ **Weight gain** ▪ Syndrome of inappropriate ADH secretion (SIADH) ▪ Bone marrow suppression ▪ Liver damage (cholestatic) ▪ Photosensitivity ▪ Hematological changes: granulocytopenia, hemolytic anemia
Contraindications	▪ Pregnancy and breastfeeding ▪ Severe cardiac, liver and kidney failure ▪ Obesity ▪ Beta-blockers (can mask hypoglycemic symptoms)

Meglitinides

Mode of action	▪ **Block the β-cell K+-ATP channel**. Act like sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site of the pancreatic channel (**Short-acting insulin secretagogues**)
Agents	▪ **Repaglinide** ▪ **Nateglinide**
Advantages	▪ The shorter action duration results in less weight gain and hypoglycaemia than sulphonylureas. ▪ Nateglinide is useful **for shift workers and patients who tend to fast for a period of time** because doses can be skipped when meals are missed. ▪ Repaglinide can be used even in CKD stages 4 and 5 without dose reduction. ▪ Useful for **post-prandial hyperglycaemia** or an **erratic eating schedule**, as patients take them shortly before meals.
Adverse effects	▪ **Weight gain and hypoglycaemia (less so than sulfonylureas)**

Thiazolidinediones (glitazones, insulin sensitizers)

Mode of action	▪ Peroxisome **P**roliferator-**A**ctivated **R**eceptor **(PPAR) gamma agonists** →↓ **products of lipid metabolism (e.g., free fatty acids)** → ↓ **free fatty acids in circulation** → increase peripheral insulin sensitivity (↓**insulin resistance**)
Agents	▪ Pioglitazone ▪ Rosiglitazone: withdrawn in 2010 due to cardiovascular side-effect.
Advantages	▪ May be used with severe renal failure (as it is metabolised by the liver) ▪ Improve dyslipidemia →↓ triglyceride, ↓ LDL, ↑ **HDL** ▪ No risk of hypoglycemia ▪ **Associated with the lowest rate of secondary beta-cell failure.** Sulfonylureas are associated with the highest rate.
Adverse effects	▪ ↑ Risk of heart failure and CVD. ↑Fluid retention and oedema **increased with insulin** drugs that cause fluid retention (e.g., **NSAIDs**, **calcium antagonists**). ▪ ↑ Risk of bone fractures (**osteoporosis**). due to **reduced osteoblast activity → reduced bone mineral density**. ▪ **Weight gain** ▪ **Bladder cancer** ▪ Liver impairment: monitor LFTs
Contraindications	▪ Congestive heart failure (NYHA III or IV) ▪ Liver failure ▪ History of **bladder cancer** or active bladder cancer; macrohematuria of unknown origin.

Insulin

Insulin Types: Overview

Type	Examples	Onset	Peak	Duration	Clinical Use
Rapid-acting	Lispro, Aspart, Glulisine	5-15 minutes	1-2 hours	3-5 hours	Used before meals for postprandial glucose control
Short-acting	Regular insulin	30-60 minutes	2-4 hours	6-8 hours	Used 30 minutes before meals; common in diabetic ketoacidosis
Intermediate-acting	NPH (Neutral Protamine Hagedorn)	1-2 hours	4-12 hours	12-18 hours	Basal insulin needs, often combined with short-acting insulin
Long-acting	Glargine, Detemir	1-2 hours (Glargine)	Minimal (steady state)	Up to 24 hours (Glargine)	Basal insulin needs; usually given once daily
Ultra long-acting	Degludec, U-300 Glargine	1-2 hours	None	>24-42 hours	Provides basal insulin; flexible timing due to long duration
Mixed insulins	Pre-mixed formulas (e.g., 70/30 NPH/Regular)	Varies	Varies	Varies	Combines short-acting and intermediate for convenience

Insulin prescription

1. **Types of Insulin for Prescription**
   - **Basal Insulin (Long-acting or Intermediate-acting)**:
     - For continuous glucose control throughout the day and night.
     - Typical starting dose: **10 units once daily** or **0.1-0.2 units/kg/day**.
     - Adjust based on fasting blood glucose (FBG) readings.
   - **Bolus Insulin (Rapid-acting or Short-acting)**:
     - For mealtime (prandial) glucose control.
     - Typically **4-6 units** or calculated based on carbohydrate intake (e.g., **1 unit per 10-15g carbs**).
   - **Premixed Insulin**:
     - Combines short and intermediate-acting insulin, administered twice daily before breakfast and dinner.
2. **Initial Dosing Strategy**
   - **Type 1 Diabetes**:
     - Start with **0.4-0.6 units/kg/day** divided as 50% basal and 50% bolus.
     - Adjust bolus based on meal carbohydrate content.

- Type 2 Diabetes:
  - Start with **10 units/day** of basal insulin if oral medications are insufficient.
  - Titrate by 2 units every 3-7 days until fasting glucose is within target.

3. **Adjustment Guidelines**
   - Adjust **basal insulin** by 2-4 units based on fasting glucose levels.
   - For **bolus insulin** adjustments, increase by 1-2 units if postprandial blood glucose is above target.
   - Use self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) to refine dosing.
4. **Insulin-to-Carbohydrate Ratio (ICR) and Correction Factor (CF)**
   - **ICR**: Estimate with **500 ÷ total daily insulin dose** for Type 1 patients.
   - **CF** (or sensitivity factor): Estimate with **100 ÷ total daily insulin dose**; each unit will lower glucose by this amount (mg/dL).
5. **Insulin Injection Sites**
   - Common sites include the abdomen, thigh, buttocks, and upper arm.
   - Rotate sites to avoid lipodystrophy.
6. **Monitoring and Follow-Up**
   - Assess HbA1c every 3 months.
   - Regular SMBG for glucose patterns, especially fasting, pre-meal, and post-meal levels.
   - Educate on hypoglycemia recognition and management (e.g., 15-15 rule).

Diabetic ketoacidosis (DKA)

Epidemiology and Pathophysiology

- **Prevalence**: 25% of type 1 diabetics present with DKA initially.
- **Pathophysiology**:
  - **Insulin deficiency** → Hyperglycemia, lipolysis → Ketogenesis → Acidosis.
  - **Osmotic diuresis** → Electrolyte loss, dehydration.
  - **Intracellular potassium deficit** despite normal or high serum potassium.

Precipitating Factors

- **Infection** (most common).
- Non-compliance with insulin.
- Newly diagnosed diabetes.
- Myocardial infarction or drugs (e.g., thiazides, steroids).

Clinical Features

- **Gastrointestinal**: Abdominal pain, nausea, vomiting.
- **Respiratory**: Kussmaul breathing, fruity (acetone) breath.
- **Electrolytes**: Potassium shifts, false hyponatremia.
- **Other**: Polyuria, dehydration, tachycardia.

Diagnosis

- **Hyperglycemia** >11 mmol/L.
- **Ketosis**: Blood ketone >3 mmol/L or ketonuria ≥2+.
- **Metabolic acidosis**: Bicarbonate <15 mmol/L or pH <7.3.

Management

1. **Fluid Replacement**:
   - **Calculate deficit**: Typically 5-8 L.
   - **0.9% NaCl** infusion at varying rates over 24 hours.
   - **Add glucose** when serum glucose falls below 14 mmol/L.
2. **Potassium Replacement**:
   - If **K+ <3.3 mmol/L**: Hold insulin and give IV potassium.
   - If **K+ 3.3-5.3 mmol/L**: Add potassium to fluids.
   - If **K+ >5.3 mmol/L**: Monitor without potassium replacement.
3. **Insulin Therapy**:
   - **Start continuous IV infusion**: 0.1 units/kg/hr.
   - **Adjust dosage**: Target glucose fall by 3 mmol/L/hr.
   - Switch to **subcutaneous insulin** upon DKA resolution.
4. **Complications**:
   - **Cerebral edema**: Treat with mannitol or hypertonic saline.
   - **DVT prophylaxis**: Use low molecular weight heparin.

Hyperosmolar Hyperglycemic State (HHS)

Pathophysiology

- **Severe hyperglycemia** without significant ketosis.
- **Dehydration** and increased osmolality due to osmotic diuresis.
- Insulin deficiency suppresses glucose metabolism but prevents ketogenesis.

Features

- Severe dehydration: Poor skin turgor, dry mucosa.
- Neurological changes: Confusion, stupor, seizures.
- Osmolarity >320 mOsm/kg, glucose >30 mmol/L.

Management

1. **Fluid Resuscitation**:
   - Start with **0.9% NaCl**; switch to **0.45% NaCl** if osmolality does not improve.
2. **Insulin Therapy**:
   - Start at **0.05 units/kg/hr** only after adequate fluid replacement.
3. **Potassium Monitoring and Replacement**:
   - Follow similar protocols as DKA.
4. **Targets**:
   - Gradual reduction of glucose (≤5 mmol/L/hr).
   - Monitor for complications: Thromboembolism, cerebral edema, osmotic demyelination.

Comparison: DKA vs. HHS

Parameter	DKA	HHS
Glucose	>11 mmol/L	>30 mmol/L
pH	<7.3	>7.3
Ketones	Present (>3 mmol/L)	Absent or minimal
Bicarbonate	<15 mmol/L	>15 mmol/L
Osmolality	Variable	>320 mOsm/kg

Hypoglycaemia

Definition

- **In diabetic patients**: Plasma glucose ≤ 3.9 mmol/L (≤ 70 mg/dL).
- Classified as:
  - **Mild**: Managed by the patient independently.
  - **Severe**: Requires assistance from a third party.

Causes

1. **Diabetic Patients**:
   - **Medication-related**: Excessive insulin or oral hypoglycemic agents.
   - **Glucose-related**: Missed meals, excessive exercise.
   - **Acute illness**: Sepsis, renal failure (↓ insulin clearance).
2. **Non-Diabetic Patients**:
   - **Insulinoma** or pancreatic tumors.
   - **Factitious hypoglycemia**: Self-administration of insulin/sulfonylureas.
   - **Alcohol use**.
   - **Adrenal insufficiency**.
   - **Gastric bypass surgery** (late dumping syndrome).

Clinical Features

- **Autonomic symptoms**:
  - **Sympathetic**: Tremors, sweating, palpitations, anxiety.
  - **Parasympathetic**: Hunger, nausea, paresthesias.
- **Neuroglycopenic symptoms**:
  - Confusion, agitation, seizures, altered behavior.
  - Nocturnal hypoglycemia → Vivid dreams, daytime fatigue.

Diagnostic Criteria: Whipple's Triad

1. **Low plasma glucose**.
2. **Typical symptoms of hypoglycemia**.
3. **Resolution of symptoms** with glucose administration.

Investigations for Non-Diabetic Hypoglycemia

- **During hypoglycemic episode**:
  - Serum **insulin** and **C-peptide** levels:
    - **↑ Insulin + ↓ C-peptide**: Exogenous insulin abuse.
    - **↑ Insulin + ↑ C-peptide**: Endogenous overproduction (e.g., insulinoma).
  - **Sulfonylurea levels** (serum/urine).
  - **Liver function tests** and **blood alcohol** level.
  - **Cortisol levels** (Synacthen test if needed).
  - **Chest X-ray** for occult malignancies.

Management

If Conscious and Able to Swallow:

1. **Oral glucose** (15–20 g) via juice or glucose tablets.
2. Recheck glucose in 15 minutes; repeat if needed (up to 3 cycles).
3. If still <4.0 mmol/L after 45 minutes → 200 mL of 10% IV glucose over 15 minutes.
4. After glucose normalizes, give **long-acting carbohydrates** (e.g., biscuits, bread, milk).

If Unconscious/Unable to Swallow:

1. **IV glucose**:
   - 100 mL of 20% glucose or 200 mL of 10% over 15 minutes.
   - Recheck glucose after 10 minutes; repeat if needed.
2. If **no IV access**: Administer **glucagon 1 mg IM** or **SC**.

Hypoglycemia Unawareness

- **Mechanism**: Recurrent hypoglycemia → blunted counter-regulatory response (HAAF).
- **Risk factors**: Type 1 diabetes, alcohol, beta-blockers, strict glycemic control.
- **Management**
  - **Optimize insulin therapy** with basal-bolus regimens.
  - **Continuous glucose monitoring (CGM)** for real-time feedback.
  - **Insulin pumps** for patients with recurrent severe hypoglycemia.
  - **Islet cell transplantation** if other treatments fail.
  - **Driving restrictions**: Stop driving for 3 months after a second severe hypoglycemic episode.

Features associated with progressive hypoglycemia		
4.4 mmol	80 mg	Decrease insulin secretion
3.9 mmol	70 mg	Increase glucagon, epinephrine, ACTH, cortisol and GH
2.8 mmol	50 mg	Palpitation, sweating
2.2 mmol	40 mg	Decrease cognition, aberrant behaviour, seizure, coma
1.1 – 0.6 mmol	10 – 20 mg	Neuronal cell death

Hypoglycaemia unawareness

- **Definition:** onset of neuroglycopenia before the appearance of autonomic warning symptoms.
- **Mechanism:** Recurrent hypoglycaemia → hypoglycemia-associated autonomic failure (HAAF) → failure of counter-regulatory hormones → inability to recognise impending hypoglycaemia by symptoms.
- **Risk factors: type-1 DM, intensively controlled diabetes of long duration Alcohol, Beta-blockers.**
- **Treatment**
  - ⇨ **Optimise insulin treatment and flexible insulin therapy using basal-bolus regimens.**
  - ⇨ **Hypoglycaemia in adults with type 1:** offer insulin pump and real-time continuous glucose monitoring.
  - ⇨ **Recurrent severe hypoglycaemia that has not responded to other treatments:** refer to islet cell transplantation.
  - ⇨ **Stop driving for 3 months after a second episode of hypoglycaemia.**

Diabetes Mellitus: Early Morning Hyperglycemia

- **Causes**
  - ⇨ Most common: nocturnal growth hormone secretion and hypoinsulinemia.
  - ⇨ **Dawn Phenomenon**: Early morning increase in growth hormone (GH) → ↑ hepatic gluconeogenesis → early-morning hyperglycemia.
  - ⇨ **Somogyi Effect**: No substantial evidence to support the theory of nocturnal hypoglycemia causing hyperglycemia via counter-regulatory hormones.
- **Diagnosis**
  - ⇨ Measure **nocturnal blood glucose**. Confirm normal glucose levels at night but elevated glucose in the early morning.
- **Treatment**
  - ⇨ Adjust the timing or increase the dose of **long-acting insulin**, under careful glycemic control.

Diabetes Mellitus: Hypertension Management

- **ACE Inhibitor**: First-line in all diabetic patients, offering renoprotective benefits.
- **African or Caribbean family origin**: ACE inhibitor + diuretic or calcium channel blocker.
- **Pregnancy or planning pregnancy**: Calcium channel blockers preferred. Nondihydropyridine agents (e.g., diltiazem, verapamil) reduce albuminuria better than dihydropyridine ones (e.g., amlodipine).
- **Avoid beta-blockers**: Routine use should be avoided as they may cause insulin resistance, impair secretion, and affect hypoglycemia responses.

Blood Pressure Targets

- **With end-organ damage** (renal disease, retinopathy): <130/80 mmHg
- **Without end-organ damage**: <140/80 mmHg

- ❖ **Antihypertensive therapy → prevent the overall risk of both microvascular and macrovascular events.**
- ❖ **Lipid-lowering therapy → prevents macrovascular events** but does not affect microvascular events.
- ❖ **Lowering HbA_{1c}** only prevents **microvascular** events.

Post prandial pain in diabetics

DM, smoking → macrovascular disease → **Mesenteric artery stenosis**. Taking a meal → ↑ **splanchnic blood flow → ↓ blood flow to the bowel → ischaemic-type pain.**

Diabetic retinopathy

Definition: a microvascular complication of diabetes damaging the eye retina.

Epidemiology

- **The most common cause of visual impairment and blindness** in age 25-65.
- **In type I DM, 80% will have retinopathy 10 years after diagnosis.**
- **In type II DM (where the onset time is uncertain), up to 25% of patients will have retinopathy at the time of diagnosis.**

Pathogenesis: Hyperglycaemia →↓ Contractile action of retinal pericytes (which regulates retinal capillary blood flow) → ↑ **retinal blood flow → Endothelial dysfunction → Exudates** due to high vascular permeability + **Microaneurysms** formation (**the earliest sign of diabetic retinopathy**) + **Neovascularization**

Features

- Asymptomatic until very late stages of disease
- Visual impairment and progression to blindness

Causes of rapid worsening of diabetic retinopathy

- **Pregnancy: needs dilated fundoscopy or photography every trimester (3 monthly).**
- **Rapid improvement in blood glucose** (suddenly dropped glucose levels → Retinal artery vasoconstriction → rapid deterioration of retinopathy)
- **Smoking →↑ risk in type 1 DM (however, it ↓ the risk type 2 DM** (a meta-analysis published in 2018).

Classification

Traditional classification	New classification
Background retinopathy • Microaneurysms (dots) • Blot haemorrhages (≤ 3) • Hard exudates **Pre-proliferative retinopathy** • Cotton wool spots (soft exudates; ischaemic nerve fibres) • > 3 blot haemorrhages • Venous beading/looping • Deep/dark cluster haemorrhages • More common in Type I DM, treated with laser photocoagulation	**Non-proliferative diabetic retinopathy (NPDR)** ▪ **Mild NPDR:** 1 or more microaneurysm ▪ **Moderate NPDR** ⇨ Microaneurysms ⇨ Blot haemorrhages ⇨ Hard exudates ⇨ Cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR ▪ **Severe NPDR** ⇨ <u>Blot haemorrhages and microaneurysms in 4 quadrants</u> ⇨ Venous beading in at least 2 quadrants ⇨ IRMA in at least 1 quadrant ▪ **Proliferative retinopathy** ⇨ More common in Type I DM, 50% blind in 5 years ⇨ Retinal neovascularization (new vessels)- may lead to vitreous haemorrhage.

Diagnosis: **fluorescein angiography**

Management

- **Glycaemic control:** (gradually **over several weeks** because sudden drop in glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy). **Target HbA1c of 47.54 mmol/mol (6.5%) → reduce progression of retinopathy.**
- **Hypertensive control (more effective than glycaemic control at reducing progression).**
- **Non-Proliferative Diabetic Retinopathy (NPDR):** regular observation and if severe, consider **pan-retinal laser photocoagulation**
- **Proliferative retinopathy**
  - ⇨ **Urgent referral to an ophthalmologist (within one week)**
  - ⇨ laser photocoagulation: **90% effective in preventing vision loss.**
  - ⇨ Intravitreal anti-vascular endothelial growth factor (VEGF) injection
  - ⇨ If severe or vitreous haemorrhage: vitreoretinal surgery.
- **Maculopathy**
  - ⇨ **More common in Type II DM.** It may occur in all stages of NPDR and PDR.
  - ⇨ **Mechanism:** Retinal vessel microangiopathy → **blood leaks** → retinal haemorrhages → **retinal infiltration with lipids and fluid** → macular oedema Hard **exudates** and macular ischemia.
  - ⇨ **Management:** responds to laser treatment at the point of leakage. If there is a change in visual acuity, then intravitreal vascular endothelial growth factor (VEGF) inhibitors.

Diabetic neuropathy

Pathophysiology: Chronic hyperglycaemia → damages small blood vessels, which supply the nerve → nerve ischaemia.

Features

- **Distal symmetric polyneuropathy is the most common form.**
- **Sensory nerves are affected more than motor.**
- **Usually associated with retinopathy and nephropathy.**
- **Large fibre** is affected first **(reduced proprioception, light pressure and vibration sensation). Short-fibre** neuropathy **is a later manifestation** (hyperparesthesia, superficial pain, impaired thermosensation, reduced sweating and a cold foot)
- **Pain** (the most common **symptom)**
- **Loss of sensation: symmetric**, in the distal lower extremities (**stocking-glove sensory loss**) → painless injuries over pressure points, most commonly on the foot, over the metatarsal heads.
- **Autonomic features**

Features of Diabetic autonomic neuropathy	
Urogenital system	• **Erectile dysfunction (most common)** • **Bladder dysfunction:** urinary retention, incomplete bladder emptying, overflow incontinence.
Cardiovascular system	• **Silent myocardial infarction** • **Decreased heart variability or fixed rhythm (Heart rate variability during breathing of < 10 beats per minute. Heart rate increase on standing of < 15 beats per minute)** • Persistent sinus tachycardia • Orthostatic hypotension
Gastrointestinal system	• **Gastroparesis:** Delayed gastric emptying due to nonmechanical obstruction → nausea, abdominal bloating, early satiety. Treatment: prokinetic agents, e.g., **metoclopramide (first-line),** erythromycin, domperidone. • **Diarrhea, constipation, incontinence**

- **Diabetic amyotrophy (proximal diabetic neuropathy):**
  - ⇨ Mixed motor and sensory proximal neuropathy, uncommon, affecting 1% of patients.
  - ⇨ Typically occurs in recently diagnosed T2DM or fairly good controlled DM. diagnosis of diabetic amyotrophy may lead to discovery of underlying DM in 30% of cases.
  - ⇨ Pain is usually the first symptom, often in the thigh, hips or buttocks, often asymmetrical. **Leg pain, weakness and reduced knee reflexes,**
  - ⇨ Diagnosis: EMG shows multifocal denervation in paraspinous & leg muscles. MRI to rule out structural lesions of the lumbosacral plexus, brachial plexus, or spinal cord.

Treatment of

- **DM control**
- **Painful neuropathy**
  - ⇨ **First-line: duloxetine, amitriptyline, gabapentin or pregabalin**
  - ⇨ **If the first-line drug treatment does not work, try one of the other 3 drugs**

Pharmacotherapy for painful diabetic neuropathy: Relevant comorbidities for drug selection

Drug class	Comorbidities favoring use	Contraindications
Serotonin-norepinephrine reuptake inhibitors (SNRIs) ▪ Duloxetine (the standard first-line therapy) ▪ Venlafaxine	▪ Depression ▪ Anxiety	▪ Restless legs syndrome ▪ Sexual dysfunction (for venlafaxine) ▪ **Angle-closure glaucoma** ▪ **patients on another serotonergic agent (e.g., tramadol) →↑ risk of serotonin syndrome.**
Tricyclic antidepressants (TCAs) ▪ **Amitriptyline** ▪ Nortriptyline ▪ Desipramine	▪ Depression ▪ Anxiety ▪ **Insomnia**	▪ **Cardiac disease** ▪ Prolonged QTc ▪ **Orthostatic hypotension** ▪ Sexual dysfunction ▪ **Urinary retention** ▪ **Angle-closure glaucoma**
Gabapentinoid anticonvulsants ▪ Pregabalin (**preferable over gabapentin if there is renal impairment**) ▪ Gabapentin	▪ Restless legs syndrome ▪ Essential tremor ▪ Insomnia	▪ Substance abuse ▪ Peripheral edema ▪ Chronic obstructive pulmonary disease

Diabetic foot

Pathophysiology: It occurs secondary to two main factors:

- **Neuropathy:** resulting in loss of protective sensation (e.g. not noticing a stone in the shoe), Charcot's arthropathy, dry skin
- **Peripheral arterial disease:** diabetes is a risk factor for both macro and microvascular ischaemia

Presentations

- **Neuropathy:** loss of sensation
- **Ischaemia:** absent foot pulses, reduced ankle-brachial pressure index (ABPI), intermittent claudication
- **Complications:** calluses, ulceration, Charcot's arthropathy, cellulitis, osteomyelitis, gangrene

Screening (at least annually)

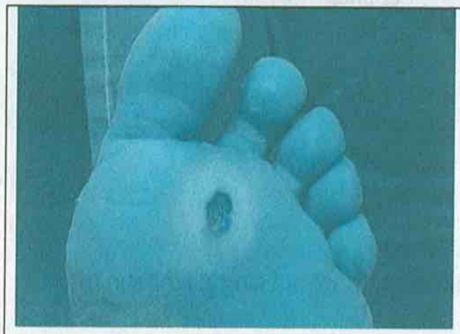
- **screening for ischaemia:** done by palpating both the dorsalis pedis pulse and posterior tibial artery pulse
- **screening for neuropathy:** a 10 g monofilament is used on various parts of the sole of the foot.

Neuropathic VS ischaemic foot

Neuropathic foot	Ischaemic foot
often warm	**Cold foot**
Painless or abnormal neuropathic pain.	causes **rest pain**
bounding pulses	nearly **pulseless foot**
ulceration tends to occur on the plantar surface	Ulceration tends to be painful and often presents in the heal area
It can be high-arched, with toe clawing.	there is often gravity-dependent reddening of the foot, which disappears on elevation of the foot.

Venous stasis ulcers:

- **Typically present in the area around the ankle.**
- **Treatment:** **Multi-layer bandaging** →↓lower limb oedema and ↑chances of healing. **An ankle brachial pressure index (ABPI) measurement is essential before beginning bandaging,** as if there is significant arterial insufficiency, the blood supply to the lower limb may be threatened.



This is a typical **neuropathic ulcer**, with callus forming the edge and a clean base.

Necrobiosis lipoidica diabeticorum

Diabetic neuropathic arthropathy (Charcot's foot)

Definition: Disrupted and damaged joint (mid-foot collapse) secondary to a loss of sensation.

Causes: **Diabetes mellitus (the most common cause)**

Pathophysiology

- **Multifactorial, due to a combination of mechanical, neuropathic and vascular**
- The commonest affected joints are the tarso-metatarsal joint and metatarsophalangeal joint.

Features

- **The foot and ankle are typically** __swollen__, __red__ **and** __warm__
- **Midfoot arch collapse** → Bony prominences on the plantar aspect with later pressure ulceration

Diagnosis

- **Exclude infections such as osteomyelitis (CRP & WBC)**
- **X-ray:** plain radiographs can be normal in the early stages. later on show joint destruction, osteolysis, joint reorganisation and subluxation.
- **MRI:** shows midfoot subchondral bone marrow oedema

Management

- **Immobilisation in a plaster cast for 3–6 months is the treatment of choice.**
- **Bisphosphonates:** bisphosphonates → reduction in bone reabsorption → accelerate healing.
- **Surgery:** reserved for severe deformities

Necrobiosis lipoidica diabeticorum

Definition: A disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition. May precede symptoms and signs of diabetes by several months.

Epidemiology: More common in females

Features: Typically, painless. **Beginning as a patch of erythema that spreads across the shin, begins to yellow and can then ulcerate.**

Diagnosis: Biopsy reveals granuloma formation with infiltration of lymphocytes, plasma cells and eosinophils.

Treatment: **Topical steroids is the most appropriate treatment to the non-atrophied areas.** the areas of already atrophied skin respond poorly to steroid therapy.

Insulinoma

Definition

- **Insulinoma** is a **rare neuroendocrine tumour** of the pancreas, derived from **beta-cells**, which causes **excessive insulin secretion** leading to **hypoglycemia**.

Epidemiology

- **Most common** cause of endogenous hyperinsulinemic hypoglycemia.
- Incidence: **1–4 cases per million annually**.
- Typically **benign** (90%) and usually **solitary** tumors; around **10%** are malignant.
- Associated with **Multiple Endocrine Neoplasia Type 1 (MEN1)** in 5-10% of cases.

Pathophysiology

- **Uncontrolled insulin secretion** leads to **hypoglycemia**, even in the fasting state.
- Tumors are usually small (<2 cm) and can occur **anywhere in the pancreas**.

Clinical Features

- **Whipple's Triad**:
  1. Symptoms of hypoglycemia (e.g., sweating, confusion, weakness).
  2. **Low blood glucose** (<50 mg/dL or <2.8 mmol/L).
  3. Symptom relief with **glucose administration**.
- **Symptoms of Hypoglycemia**:
  - **Neurogenic:** Palpitations, tremors, anxiety, and sweating.
  - **Neuroglycopenic:** Confusion, dizziness, seizures, blurred vision, and in severe cases, coma.

Diagnosis

- **Biochemical Tests:**
  - **72-hour fasting test**: Monitors glucose and insulin levels during prolonged fasting.
  - **Elevated insulin** despite low glucose.
  - **C-peptide levels:** Elevated, indicating endogenous insulin production (distinguishing from exogenous insulin use).
  - **Proinsulin levels**: Typically elevated in insulinoma.
- **Imaging Studies:**
  - **CT or MRI scan**: Localizes the tumor.
  - **Endoscopic Ultrasound (EUS)**: Highly sensitive for detecting small tumors.
  - **Selective Arterial Calcium Stimulation Test (SACST):** Used when imaging is inconclusive.

Management

- **Surgical Resection**:
  - First-line treatment for **benign tumors**.
  - **Enucleation** or partial pancreatectomy depending on the tumor location.
- **Medical Management**:
  - Used for **inoperable or malignant insulinomas**:
    - **Diazoxide**: Inhibits insulin release.
    - **Octreotide (Somatostatin analogs)**: Reduces insulin secretion in some patients.
    - **Glucagon injections**: For emergency treatment of severe hypoglycemia.
- **Chemotherapy or Radiotherapy**:
  - For **malignant cases** with metastasis.

Glucagonoma

Overview

- A rare neuroendocrine tumour that secretes glucagon.
- Usually solitary, and the majority are located in the distal pancreas.
- Frequently malignant and slow-growing but usually advanced by the time of diagnosis (50 - 80% are metastatic at presentation)

Features

Glucagonoma → 6 Ds

1. **Decreasing weight** (due to protein catabolism)
2. **Diabetes** (glucose intolerance)
3. **Dermatitis** (necrolytic migratory erythema): Red, blistering rash. Most common (75% of cases)
4. **Diarrhoea** (chronic)
5. **DVT** (venous thrombo-embolism)
6. **Depression** (neuropsychiatric features)

Diagnosis
- **Confirmation: Elevated fasting plasma glucagon level** (>500 pg/mL).
- **Tumor localization and staging**: contrast-enhanced CT or MRI.

Management
- Somatostatin analogues (eg, octreotide) → improves the skin rash and diarrhoea
- **Localized tumour to the pancreas** (only 5%): resection
- **Hepatic metastatic disease** (without bilobar involvement, ↓liver function, or extrahepatic metastases): hepatic resection (if fit for surgery) or Hepatic arterial embolization with or without selective hepatic artery infusion of chemotherapy (if unfit)
- **Extrahepatic metastases or unresectable disease:** Somatostatin analogs (eg, octreotide)

Maturity-onset diabetes of the young (MODY)

Definition
- **Monogenic diabetes** characterized by early onset of hyperglycemia (before 25 years) due to a **single gene mutation** affecting insulin secretion.
- It has **autosomal dominant inheritance**, meaning it often runs in families across generations.

Types and Genetic Causes

Type	Gene Mutated	Key Characteristics
MODY 1	HNF4A	Progressive hyperglycemia, often misdiagnosed as type 1 or 2 diabetes. Responsive to **sulfonylureas**.
MODY 2	GCK (Glucokinase)	Mild fasting hyperglycemia from birth; rarely requires treatment.
MODY 3	HNF1A	Most common form, presents with significant hyperglycemia, typically responds well to **low-dose sulfonylureas**.
MODY 4	PDX1 (IPF1)	Rare; associated with pancreatic agenesis and insulin deficiency.
MODY 5	HNF1B	Often involves **renal abnormalities** and may require insulin.
MODY 6	NEUROD1	Linked with impaired insulin secretion and sometimes neurological issues.

Clinical Features
- **Early-onset diabetes** (before 25 years).
- **Family history** of diabetes spanning multiple generations.
- **Lack of autoimmunity** or insulin resistance (distinguishing it from type 1 and type 2 diabetes).
- Varies from **mild fasting hyperglycemia** (MODY 2) to more **severe hyperglycemia** (MODY 1, 3).

Diagnosis
- **Genetic testing**: Confirms the specific gene mutation responsible.
- **Fasting glucose** and **HbA1c**: May show mild or moderate hyperglycemia.
- **C-peptide levels**: Help differentiate MODY from type 1 diabetes (as C-peptide levels are not depleted).
- **Family history evaluation**: Important to assess the inheritance pattern.

Management

- **MODY 1, 3:** Often respond well to **sulfonylureas** (e.g., gliclazide) instead of insulin.
- **MODY 2:** May not require treatment, just lifestyle changes and glucose monitoring.
- **MODY 5:** Insulin therapy often needed due to progressive insulin deficiency.
- **Monitoring for complications**: Particularly with MODY 5 (renal issues) and MODY 3 (risk of vascular complications).

Latent autoimmune diabetes of adulthood (LADA)

Definition: a late onset of type 1 (autoimmune) diabetes often mistaken for type 2 diabetes.

Epidemiology: 10% of patients are incorrectly labelled as type 2 diabetic.

Feature

- **Features consistent with type 1 diabetes (eg, weight loss)** but with slow progression of autoimmune-cell failure (thus insulin not usually required in the early stages)
- In contrast to type 2 diabetes, patients are typically **younger**, have **low BMI**, with a **history of autoimmune disease** (personal or family)

Diagnosis: Anti-glutamic acid Decarboxylase (**GAD**) or anti-pancreatic islet-cell (**ICA**) **antibodies**

Management

- **Early use of insulin** may prolong beta-cell function
- **Sulphonylureas should not be used** (it may lead to a more rapid progression)

Mitochondrial diabetes

Aspect	Details
Definition	A rare form of diabetes caused by **mitochondrial DNA (mtDNA) mutations**, often coexisting with multisystem disorders.
Inheritance	**Maternal inheritance** – mitochondria are transmitted from mother to offspring.
Common Features	- **Diabetes symptoms**: Hyperglycemia, fatigue, weight loss. - **Hearing impairment**: Sensorineural hearing loss. - **Neurological symptoms**: Stroke-like episodes, epilepsy, muscle weakness.
Diagnosis	- **Genetic testing** for mtDNA mutations (e.g., **m.3243A>G mutation**). - **Hearing evaluation** to detect sensorineural hearing loss. - **Blood tests** to monitor glucose and insulin levels.
Management	- **Initial treatment**: Oral hypoglycemics (e.g., metformin). - **Progressive cases**: Insulin therapy. - **Hearing aids or cochlear implants** for hearing loss. - **Monitoring** for complications (e.g., cardiomyopathy, neurological involvement).
Prognosis	Progressive condition; insulin may be required with time. High risk of **organ dysfunction** and **neurological complications**.

Diabetes in pregnancy

Classification

- **Gestational Diabetes Mellitus (GDM):**
  - Diabetes diagnosed between **24-28 weeks** of pregnancy.
  - Early diagnosis indicates **undiagnosed type 2 diabetes.**
- **Pre-existing Diabetes:**
  - **Type 1 or Type 2 Diabetes** present before pregnancy.

Gestational Diabetes Mellitus (GDM): screening and diagnosis

Risk Factors	Screening	Diagnosis
- BMI >30 kg/m² - Previous macrosomic baby (>4.5 kg) - Previous GDM - Family history of diabetes - Ethnic groups: South Asian, Black Caribbean, Middle Eastern	- **Previous GDM:** OGTT as early as possible and at 24-28 weeks if initial test is normal. - **Other risk factors:** OGTT at 24-28 weeks.	- **Fasting glucose ≥ 5.6 mmol/L** - **2-hour OGTT ≥ 7.8 mmol/L** - If fasting glucose 5.5–7.0 mmol/L → 75-g OGTT recommended.

GDM complications and management

Complications	Management
- **Macrosomia** (birth weight >4.5 kg) leading to shoulder dystocia. - **Neonatal hypoglycaemia.** - **Maternal:** Hypertension, preeclampsia, increased cesarean risk, risk of future diabetes.	- **Aspirin 75 mg/day** to prevent preeclampsia. - **Fasting glucose < 7 mmol/L:** Diet and exercise trial. - If targets unmet after 1-2 weeks → Add **metformin**. - If still uncontrolled → Add **insulin**. - If **fasting glucose ≥ 7 mmol/L** → Start insulin. - **Postpartum monitoring:** Check fasting glucose and HbA1c at 6-13 weeks postpartum.

Pre-existing Diabetes in Pregnancy

Complications	Management
- **Congenital malformations** risk increased 2-fold. - Risk of **miscarriage, stillbirth**, and neonatal death.	- **Pre-conception:** Optimize glucose control. - Stop oral hypoglycemics (except **metformin**) and switch to **insulin**. - **Folic acid 5 mg/day** pre-conception to 12 weeks. - **Aspirin 75 mg/day** from 12 weeks to delivery. - **Anomaly scan at 20 weeks** (focus on heart anatomy). - Monitor and treat **retinopathy** during pregnancy. - Use **Continuous Glucose Monitoring (CGM)** for better control.

Glucose Targets for Pregnant Women (Pre-existing and GDM)

Timing	Target Glucose Level
Fasting	≤ 5.3 mmol/L
1 hour post-meal	≤ 7.8 mmol/L
2 hours post-meal	≤ 6.4 mmol/L

Obesity and Lipids disorders

Obesity

Obesity Classification

Classification	Body Mass Index (BMI) kg/m²
Healthy weight	18.5-24.9
Overweight	25-29.9
Obesity I	30-34.9
Obesity II	35-39.9
Obesity III (Morbid obesity)	40 or more

Obesity: management (step-wise approach)

First-line: Lifestyle Modifications

Intervention	Details
Dietary Changes	**Calorie Deficit:** 500–1000 kcal/day reduction. **Diet Plans:** Mediterranean, DASH, or low-carb diet.
Physical Activity	**Goal:** 150–300 minutes of moderate aerobic activity per week (e.g., walking, swimming). **Strength Training:** At least twice a week.
Behavioral Therapy	Use **CBT techniques** for emotional eating. Tools: Food diaries, weight tracking apps, and self-monitoring.

Second-line: Pharmacologic Therapy

Drug	Mechanism	Dose	Side Effects / Monitoring
Orlistat	Inhibits fat absorption via lipase inhibition.	**120 mg** three times daily with meals.	Gastrointestinal effects (oily stools). Monitor fat-soluble vitamins (A, D, E, K).
Liraglutide	GLP-1 receptor agonist; suppresses appetite.	**3.0 mg SC injection daily** (titrate from 0.6 mg over 4 weeks).	Nausea, vomiting, pancreatitis. Monitor glucose in diabetes.
Phentermine/Topiramate	Suppresses appetite and hunger.	**Start:** 3.75/23 mg daily; **Max:** 15/92 mg daily.	Insomnia, dry mouth. Avoid in pregnancy and CVD.
Naltrexone/Bupropion	Reduces food cravings and appetite.	**32 mg/360 mg daily** in divided doses.	Mood changes; contraindicated in hypertension and seizure disorders.

- **Discontinue** if weight loss is <5% after 3 months.

Third-line: Bariatric Surgery

Criteria	Details
Indications	BMI ≥40 kg/m² or BMI ≥35 kg/m² with comorbidities (e.g., diabetes, CVD).
Types of Surgery	- **Roux-en-Y Gastric Bypass:** Restriction + malabsorption. - **Sleeve Gastrectomy:** Reduces stomach size. - **Adjustable Gastric Banding:** Reversible option.
Follow-up	Lifelong **nutritional monitoring** for vitamin B12, calcium, and iron deficiencies.
Vitamin Supplementation	**Multivitamins, calcium, vitamin D, iron supplements** as needed.

Familial Hyperlipidaemia

	Aetiology	Lipid profile	Notes
Familial hyper-Chylomicronaemia	**Deficiency of Apo CII or LPL** (lipoprotein lipase)	↑ chylomicrons	typically presents with **eruptive xanthoma, abdominal colic. acute pancreatitis**
Familial hypercholesterolaemia	LDL-receptor deficiency	↑TC > 7.5 ↑LDL-C > 4.9	**Heterozygous** type is Common **Associated with tendon xanthoma**
Familial Combined Hyperlipidaemia	**overproduction of apo B-100 &(VLDL) by the liver**	↑ LDL ↑VLDL ↑TG	**The commonest type** (two thirds). Associated with glucose intolerance.
Remnant hyperlipidaemia (dysbetalipoproteinaemia)	**Abnormal ApoE**	↑ IDL	**palmar xanthoma is diagnostic** fibrates are first line treatment
Familial hypertriglyceridaemia	Overproduction or↓catabolism of VLDL (**due to ↓ LPL**)	↑TG ↑VLDL	often "polygenic". **Common**

Familial Combined Hyperlipidemia (FCHL)

- **Prevalence:** Most common type (affects 1% of population).
- **Genetics:** Autosomal dominant (polygenic) → Defective LDL receptors or ApoB-100.
- **Features:**
  - ↑ LDL, VLDL, triglycerides.
  - Xanthelasma, glucose intolerance, premature cardiovascular disease.
- **Management:**
  - **Statins** (e.g., atorvastatin) are the first-line treatment.

Remnant Hyperlipidemia (Dysbetalipoproteinemia)

- **Genetics:** Autosomal recessive → Defective ApoE → accumulation of IDL and chylomicron remnants.
- **Features:**
  - ↑ Total cholesterol, triglycerides, chylomicrons, VLDL.
  - **Xanthomas:** Palmar and tubero-eruptive xanthomas.
  - Premature atherosclerosis.
- **Diagnosis:** Lipoprotein electrophoresis or **ApoE genotyping**.
- **Management:**
  - **Fibrates** (first line) → activate PPAR-α, enhancing lipoprotein lipase activity.

Familial Hypertriglyceridemia (FHTG)

- **Genetics:** Autosomal dominant (polygenic) → Decreased lipoprotein lipase activity.
- **Features:**
  - ↑ VLDL and triglycerides with normal LDL and total cholesterol.

- **Complications:** Premature atherosclerosis, acute pancreatitis (if TG >11 mmol/L).
- **Signs:** Eruptive xanthomas, lipaemia retinalis, retinal vein thrombosis, glucose intolerance.

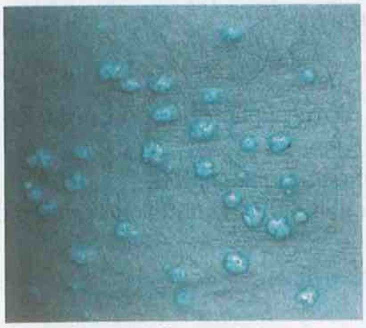
- **Management:**
  - **Fibrates** (first line).

Familial Hypercholesterolemia (FH)

- **Prevalence:** Affects 1 in 500 people.
- **Genetics:** Autosomal dominant → Defective LDL receptors.
- **Features:**
  - ↑ LDL > 4.9 mmol/L, ↑ Total cholesterol > 7.5 mmol/L.
  - **Xanthomas:** Tendon xanthomas (Achilles tendon), xanthelasma.
  - Premature coronary artery disease (<60 years).
- **Management:**
  - **High-dose statins** (aim for 50% reduction in LDL).
  - **Ezetimibe** (if statin intolerance or contraindications).
  - **Bile acid sequestrants or fibrates** (if both statins and ezetimibe are ineffective).
  - **PCSK9 inhibitors** (e.g., alirocumab, evolocumab) for high-risk patients.
  - **LDL Apheresis** or **Liver transplantation** for severe cases.
  - **Screening:** First-degree relatives have a 50% chance of being affected. Screen children ≥10 years if one parent is affected, or ≥5 years if both parents are affected.
  - **Lifestyle Changes:** Fat intake ≤30%, saturated fats ≤10%, and dietary cholesterol <300 mg/day.

Key Points:

1. **Familial Hypercholesterolemia (FH):** Most common genetic dyslipidemia, associated with early atherosclerosis.
2. **Familial Combined Hyperlipidemia (FCHL):** Mixed dyslipidemia with variable presentation.
3. **Dysbetalipoproteinemia:** Unique for presenting with palmar and tuberous xanthomas.
4. **Familial Hypertriglyceridemia (FHTG):** Significant risk of **pancreatitis**, less impact on CAD.
5. **Familial Chylomicronemia Syndrome (FCS):** Rare and severe, with **lifelong triglyceride elevation** and high pancreatitis risk.



Eruptive xanthomata

Eruptive xanthomas → Familial hypertriglyceridaemia or Familial hyper-Chylomicronaemia

Tendon xanthomata → Familial hypercholesterolaemia

Palmar xanthoma → Remnant hyperlipidaemia (dysbetalipoproteinaemia)

Secondary Hyperlipidemia

Causes

Type	Details
Predominantly Hypertriglyceridemia	- **Obesity:** **Commonest cause**; ↓ lipoprotein lipase activity, ↑ VLDL production. - **Type 2 Diabetes:** Poor glycemic control → ↓ lipoprotein lipase activity (insulin-dependent). ↑ TG, ↓ HDL (common), LDL not typically elevated. - **Alcohol, Chronic renal failure, Liver disease.** - **Drugs:** Thiazides, beta-blockers, unopposed estrogen.
Predominantly Hypercholesterolemia	- **Nephrotic Syndrome.** - **Cholestasis.** - **Hypothyroidism:** Improves with thyroxine but statins may be needed.

Complications

- **Cardiovascular Disease (CVD):** Increased risk of events.
- **Insulin Resistance:** Can worsen metabolic control.

Management

Primary Prevention (No CVD):

- **QRISK2 Score ≥ 10%:** Atorvastatin 20 mg + lifestyle changes.
- **Type 1 Diabetes:** Atorvastatin 20 mg for patients >40 years, diabetes duration >10 years, or nephropathy.
- **Type 2 Diabetes:** Atorvastatin 20 mg (JBS2 guidelines recommend statins for all T2DM patients regardless of cholesterol levels).
- **CKD:** Atorvastatin 20 mg.

Secondary Prevention (Established CVD):

- **All patients:** Atorvastatin 40 mg.
- **Follow-up:** If non-HDL cholesterol hasn't decreased by 40% after 3 months → increase dose up to 80 mg.

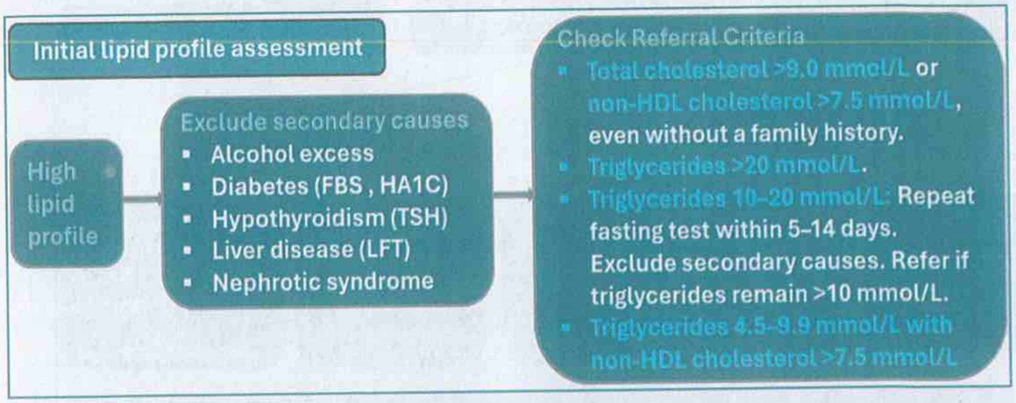
Hypertriglyceridemia:

1. **If TG > 20 mmol/L:**
   - Exclude familial hypertriglyceridemia.
   - **Fibrates** (e.g., fenofibrate) as first-line therapy.
2. **If TG 10–20 mmol/L:**
   - Repeat fasting lipid profile.
   - Address secondary causes and lifestyle factors (e.g., weight loss, healthy diet, exercise).
   - **Statins** (e.g., atorvastatin, rosuvastatin) for persistent high TG.
   - Add **Omega-3 Fatty Acid Ethyl Esters** or fibrates if TG remains elevated despite statins.

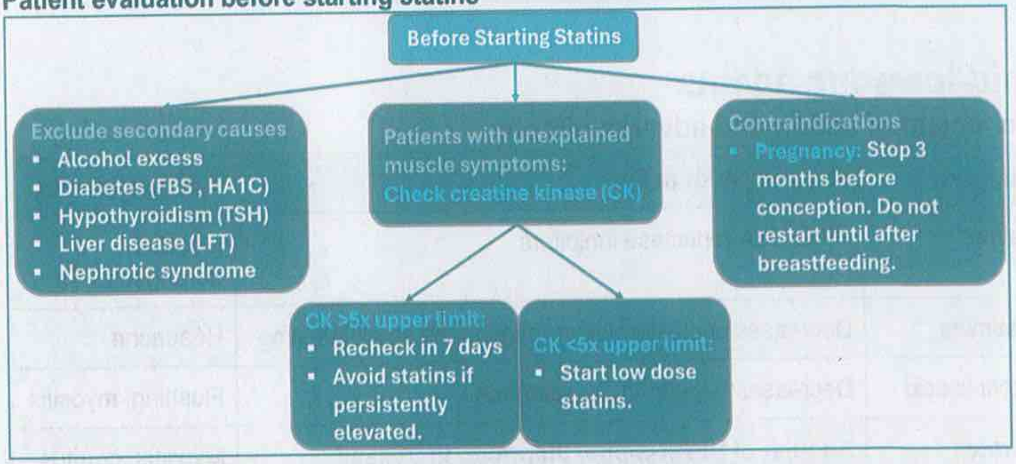
Treatment Targets (Joint British Societies Guidelines)

Parameter	Target
Total Cholesterol	< 4.0 mmol/L
LDL Cholesterol	< 2.0 mmol/L
Triglycerides	< 1.7 mmol/L

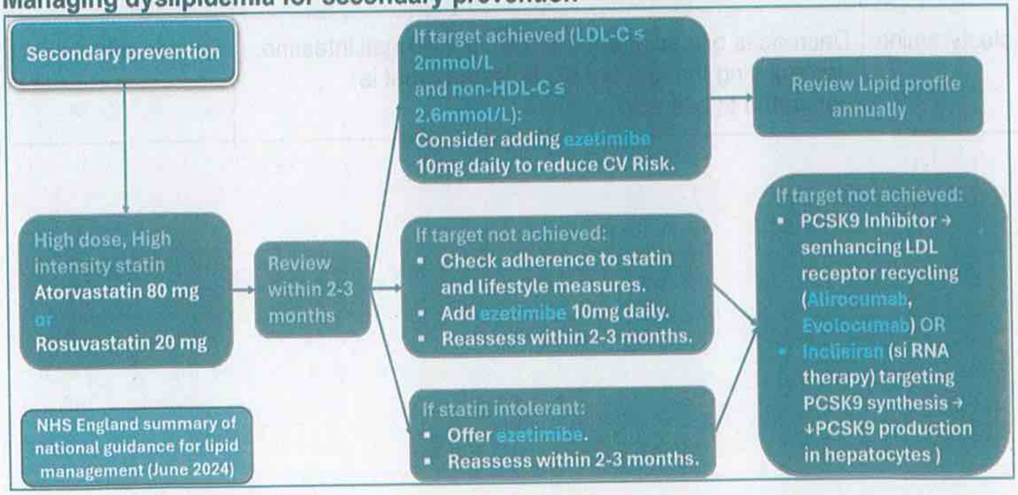
Initial evaluation of dyslipidemia



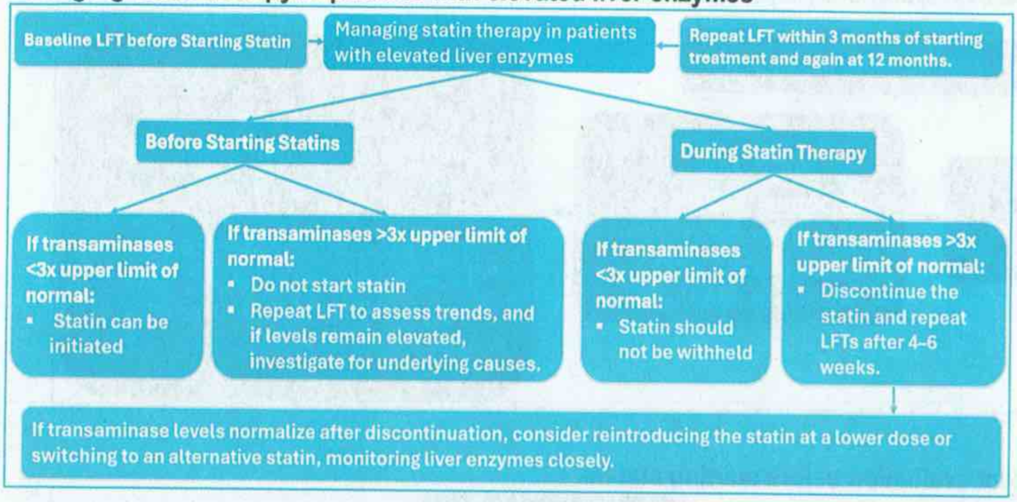
Patient evaluation before starting statins



Managing dyslipidemia for secondary prevention



Managing statin therapy in patients with elevated liver enzymes



Lipid-lowering agents

Mechanism of action and adverse effects

Drugs	Mechanism of action	Adverse effects
Statins	HMG CoA reductase inhibitors	Myositis, deranged LFTs
Ezetimibe	Decreases cholesterol absorption in the small intestine	Headache
Nicotinic acid	Decreases hepatic VLDL secretion	Flushing, myositis
Fibrates	**Agonist of PPAR-alpha, therefore, increases lipoprotein lipase expression.**	Myositis, pruritus, cholestasis
Cholestyramine	Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid	GI side-effects

Statins

Category	Details
Action	Inhibits **HMG-CoA reductase**, reducing **hepatic cholesterol synthesis**.
Examples	**Pravastatin** (for primary prevention), **Rosuvastatin** (for high-risk secondary prevention).
Adverse Effects	- **Myopathy** (5%): Myalgia, myositis, rhabdomyolysis. - More common in **lipophilic statins** (e.g., simvastatin, atorvastatin). - **Hepatotoxicity:** ↑ LFTs, discontinue if 3x upper limit of normal. - **Intracerebral hemorrhage risk:** Avoid in stroke patients.
Monitoring	Check **CK** and **LFTs** at baseline, 3 months, and 12 months.
Drug Interactions	- **P450 inhibitors** (e.g., macrolides, azoles, grapefruit juice) increase risk of myopathy. - Interaction with fibrates, nicotinic acid, and calcium channel blockers can increase myopathy risk.
Contraindications	Active liver disease, muscle disorders, pregnancy (stop 3 months before conception, avoid while breastfeeding).
Statins in Pregnancy	Stop statins before pregnancy; Omega-3 or BAS (e.g., cholestyramine) are safer alternatives.
Lowest Risk of Rhabdomyolysis	**Fluvastatin.**

Statin Intensity Classification:

Intensity Level	Statin (Daily Dose)	Approximate LDL-C Reduction
Low-Intensity	- Simvastatin 10 mg - Pravastatin 10–20 mg - Lovastatin 20 mg - Fluvastatin 20–40 mg	<30%
Moderate-Intensity	- Atorvastatin 10–20 mg - Rosuvastatin 5–10 mg - Simvastatin 20–40 mg - Pravastatin 40–80 mg - Lovastatin 40 mg - Fluvastatin XL 80 mg	30% to <50%
High-Intensity	- Atorvastatin 40–80 mg - Rosuvastatin 20–40 mg	≥50%

Statins: unique characteristics

Statin	Metabolism	Solubility	Notable Features
Atorvastatin	Hepatic via CYP3A4	Lipophilic	High-intensity statin; can be taken any time of day; potential interactions with CYP3A4 inhibitors.
Rosuvastatin	Minimal hepatic metabolism	Hydrophilic	High-intensity statin; can be taken any time of day; fewer drug interactions; effective in severe hypercholesterolemia.
Simvastatin	Hepatic via CYP3A4	Lipophilic	Moderate-intensity statin; recommended to take in the evening; higher risk of drug interactions; dose limitations with certain medications.
Pravastatin	Non-CYP metabolism	Hydrophilic	Lower risk of drug interactions; preferred in patients with polypharmacy; can be taken any time of day.
Lovastatin	Hepatic via CYP3A4	Lipophilic	Should be taken with the evening meal; higher risk of drug interactions; extended-release form available.
Fluvastatin	Hepatic via CYP2C9	Lipophilic	Available in extended-release form; lower potency; can be taken any time of day.

Statin: Cautions and Contraindications

Do Not Prescribe Statins To	Details
Active liver disease	Contraindicated.
Transaminase levels ≥3x upper limit of normal	Contraindicated due to risk of liver damage.
Pregnant or breastfeeding women	Statins are teratogenic and not recommended during breastfeeding.
Women of childbearing potential	Require adequate contraception during treatment and for 1 month after discontinuation.
Rosuvastatin-specific contraindications	- Personal/family history of hereditary muscular disorders. - Stage 4 or 5 CKD (eGFR <30 mL/min/1.73 m²). - Rosuvastatin 40 mg: Avoid in predisposed individuals (e.g., Asian ethnicity, stage 3 CKD, hypothyroidism).

Use Statins with Caution in

- History of liver disease.
- Predisposition to **rhabdomyolysis**:
  - Elderly, females, or individuals with a history of muscular disorders, hypothyroidism, or high alcohol intake.
  - Concurrent use of interacting drugs.
- History of **haemorrhagic stroke**

Statins: Adverse Effects

Category	Common Examples
Common/Very Common	Myalgia, headache, GI discomfort, dizziness, sleep disorders, thrombocytopenia, constipation, diarrhoea.
Uncommon	Alopecia, hepatic disorders, memory loss, pancreatitis, paraesthesia, skin reactions.
Rare/Very Rare	Myopathy, rhabdomyolysis, lupus-like syndrome, interstitial lung disease, tendon disorders, neuropathy.
Atorvastatin-Specific	Hyperglycaemia, hypersensitivity, nasopharyngitis, epistaxis, laryngeal pain.
Rosuvastatin-Specific	Arthralgia, haematuria, Stevens-Johnson syndrome.
Simvastatin-Specific	Acute kidney injury, anaemia, cognitive impairment, visual disturbances.

Statins: Drug Interactions

Interacting Drug/Class	Effect and Recommendation
Amiodarone, colchicine, ezetimibe	Increases risk of rhabdomyolysis; monitor or adjust dose.
Fibrates	Use with caution; adjust statin dose.
Fusidic acid	Avoid concurrent use; restart statin 7 days after fusidic acid completion.
Grapefruit juice	Avoid with simvastatin and large quantities with atorvastatin.
Azole antifungals	Avoid or adjust statin dose; monitor for rhabdomyolysis and hepatotoxicity.
HIV protease inhibitors	Avoid or adjust dose; monitor closely for rhabdomyolysis.
Ciclosporin	Avoid with rosuvastatin and simvastatin; monitor atorvastatin dose.
Warfarin	Rosuvastatin and simvastatin may enhance warfarin effects; monitor INR closely.
Combined oral contraceptives (COCs)	Consider alternative contraception in high CVD risk patients due to cardiovascular event risk.

Statins: Monitoring

Parameter	Timing and Details
Liver Function Tests	Baseline, at 3 months, and at 12 months. Discontinue if transaminases ≥3x upper limit of normal.
Creatine Kinase (CK)	Baseline in high-risk individuals; repeat if muscle symptoms (pain, tenderness, weakness) occur.
Lipid Profile	Baseline, 4–6 weeks after initiating therapy, then annually to assess efficacy and adherence.
Other Considerations	Monitor for adverse effects (e.g., muscle toxicity, interstitial lung disease) and adjust treatment accordingly.

Fibrates

Category	Details
Examples	**Bezafibrate, Fenofibrate, Gemfibrozil**.
Action	Activates **PPAR-α** → ↓ LDL, ↑ HDL, ↓↓↓ Triglycerides. Enhances lipoprotein lipase activity.
Indications	Second-line therapy for hyperlipidemia; most effective for reducing triglycerides.
Contraindications	**Renal insufficiency, liver failure, gallbladder diseases.**
Side Effects	Dyspepsia, myopathy, **cholelithiasis** (cholesterol gallstones), ↑ **LFTs** (hepatotoxicity).
Drug Interactions	Enhances effect of other drugs (e.g., **sulfonylureas, warfarin**) by inhibiting CYP450.

Omega-3 Fatty Acids

Category	Details
Example	**OMACOR** (omega-3-acid ethyl esters).
Action	Increases **peroxisomal beta-oxidation** of fatty acids in the liver → ↓ Triglyceride levels.
Indications	Recommended in combination with statins for **high-risk patients** with persistent hypertriglyceridemia.
Side Effects	**GI upset**, ↑ **bleeding time** (caution with anticoagulants).
Dose	1 capsule (460 mg) daily for secondary hypertriglyceridemia; 2 capsules for primary hypertriglyceridemia.

Ezetimibe

Ezetimibe (10 mg daily)	
Mode of action	**Inhibits the intestinal absorption of cholesterol → ↓ LDL**
Indications	▪ **Primary hypercholesterolaemia (if statin inappropriate or not tolerated)**
Adverse effects	▪ **Gastrointestinal discomfort (commonly diarrhoea)** ▪ Hepatic: Increased serum transaminases ▪ Neuromuscular & skeletal: Arthralgia (3%) ▪ Respiratory: Sinusitis (3%), upper respiratory tract infection (4%)
Contraindications	▪ active hepatic disease or transaminases ▪ active peptic ulcer ▪ arterial hemorrhage

Bempedoic Acid

Aspect	Details
Class	Adenosine triphosphate citrate lyase (ACL) inhibitor.
Mechanism of Action	Inhibits ACL, an enzyme upstream of HMG-CoA reductase, reducing cholesterol synthesis in the liver.
Indications	- Primary hypercholesterolemia (including familial hypercholesterolemia). - Mixed dyslipidemia for patients requiring additional LDL-C lowering alongside other therapies. - Used in combination with statins or ezetimibe for statin-intolerant patients or those at high CVD risk.
Dose	180 mg once daily, oral tablet.
Efficacy	Reduces LDL-C by approximately 15–25%.
	- Can be combined with ezetimibe or PCSK9 inhibitors for enhanced LDL-C reduction.
Adverse Effects	**- Common:** Hyperuricemia, gout, abdominal pain, diarrhoea, elevated liver enzymes, back pain, nasopharyngitis. **- Uncommon:** Myalgia, tendon rupture, increased creatinine kinase.
Contraindications	- Severe Hepatic Impairment - Pregnancy and Breastfeeding
Cautions	- Gout or Hyperuricemia - Tendon Disorders

PCSK9 Inhibitors

Aspect	Details
Examples	Alirocumab, Evolocumab
Mechanism of Action	Monoclonal antibodies inhibiting PCSK9 → Prevents LDL receptor degradation, enhancing LDL receptor recycling, increasing LDL-C clearance by the liver → lowering LDL-C levels.
Indications	- Primary hypercholesterolemia (familial or non-familial) - High-risk ASCVD patients failing LDL-C targets with statins ± ezetimibe - Familial hypercholesterolemia or statin intolerance - Homozygous familial hypercholesterolemia (Evolocumab only)
Administration	- Subcutaneous injection: - Alirocumab: 75–150 mg every 2 weeks or 300 mg every 4 weeks - Evolocumab: 140 mg every 2 weeks or 420 mg monthly
Efficacy	- LDL-C reduction: 50–60% - Reduces major adverse cardiovascular events (e.g., myocardial infarction, stroke)
Adverse Effects	- Common: Injection site reactions, nasopharyngitis, flu-like symptoms - Rare: Hypersensitivity, neurocognitive effects
Contraindications	- Hypersensitivity to the drug - Not recommended during pregnancy or lactation

Inclisiran

Aspect	Details
Mechanism of Action	Small interfering RNA (siRNA) therapy targeting PCSK9 synthesis → Inhibits PCSK9 production in hepatocytes at the genetic level → ↑LDL receptor recycling and LDL clearance.
Indications	- Primary hypercholesterolemia - High-risk ASCVD patients or familial hypercholesterolemia not achieving LDL-C targets with statins ± ezetimibe.
Administration	- Subcutaneous injection: 284 mg initially, at 3 months, and every 6 months thereafter.
Efficacy	- LDL-C reduction: Approximately 50–60%.
Adverse Effects	- Common: Injection site reactions, mild flu-like symptoms - Rare: Hypersensitivity reactions, liver enzyme elevation
Contraindications	- Hypersensitivity to the drug. - Not recommended during pregnancy or lactation due to limited safety data.
Advantages	- Sustained LDL-C reduction with biannual dosing. - Suitable for patients non-adherent to more frequent dosing schedules.

Nicotinic acid (niacin)

Nicotinic acid (niacin or vitamin B3) (1.5 to 3 g daily): limited by multiple side effects	
Mode of action	Inhibits lipolysis and fatty acid release in peripheral adipose tissue → ↓ triglyceride and LDL synthesis, ↑ HDL (**raise HDL cholesterol level by a great amount**)
Indications	▪ **High LDL** cholesterol despite statin and ezetimibe therapy (or if statins are contraindicated) ▪ **Low HDL** (very effective at raising HDL cholesterol)
Adverse effects	▪ **Vasodilatation → Contraindicated in cardiovascular instability (e.g. MI , angina)** ▪ **Flushing** ▪ **Hyperglycemia** (impaired glucose tolerance) →↑ HA1c in diabetics (not preferred in DM) ▪ Irritates the gastric mucosa and exacerbates gastroesophageal reflux. (**contraindicated in active peptic ulcer disease & GI bleeding**) ▪ Myositis ▪ **Hyperuricemia** → precipitates acute gout (**contraindicated in gout**) ▪ ↑ **LFTs** (**contraindicated in Liver in severe impairment**)
Contraindications	▪ active hepatic disease or transaminases ▪ active peptic ulcer ▪ arterial hemorrhage

Cholestyramine

Cholestyramine (4 g daily; each powder sachet should be mixed with at least 150 mL of water or fruit juice)	
Mode of action	(**bile acid sequestrant**) → binds bile acids in the intestine → prevents reabsorption and recycling (↓ bile acid absorption and ↑ bile acid excretion) → forces liver to consume cholesterol in the process of making more bile salts (**interruption of enterohepatic circulation**) → ↓ LDL-C
Indications	▪ Combination treatment with statins in hypercholesterinemia ▪ Pruritus associated with elevated bile acid levels (cholestasis) ▪ Bile acid diarrhoea ▪ Diarrhoea associated with Crohn's disease, ileal resection
Adverse effects	▪ Abdominal cramps and constipation ▪ **Vitamin deficiencies (↓absorption of fat-soluble vitamins** A, D and K) → night blindness (vit A), Bleeding tendency, hypoprothrombinaemia (vit K), osteoporosis (vit D): consider supplementation ▪ May raise the level of triglycerides
Contraindications	▪ **Hypertriglyceridemia (not effective)** ▪ **Complete biliary obstruction (not effective)**

Abetalipoproteinemia

Category	Details
Pathophysiology	- **Rare autosomal recessive disorder** caused by a mutation in the **microsomal triglyceride transfer protein (MTP)**. - Results in deficiency of **apolipoprotein B-48 and B-100**, impairing chylomicron formation and fat absorption. - Deficiency of **LDL, VLDL, and chylomicrons**.
Clinical Features	- **Infancy:** Steatorrhea, abdominal distension, failure to thrive. - **Childhood/Adolescence:** Progressive **ataxia**, neuropathy, and vision impairment. - **Neurologic Symptoms:** Cognitive decline, clumsiness (early sign). - **Visual Impairment:** Low acuity due to **retinitis pigmentosa** and **vitamin A deficiency**.
Treatment	- High-dose **vitamin E** supplementation. - Supplementation with other **fat-soluble vitamins (A, K, D)**. - **Dietary restriction** of long-chain fatty acids.
Causes of Hypocholesterolemia	**Acquired:** Malignancy, malabsorption syndromes, chronic infections, severe illness, and anemia. **Genetic:** - **Hypobetalipoproteinemia** (most common genetic cause). - **Abetalipoproteinemia**.

Gonads disorders

Gynaecomastia

Definition

- Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an **increased oestrogen: androgen ratio**.

Causes

- It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, **Klinefelter's (47, XXY karyotype)**
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. **seminoma** secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- starvation/refeeding
- drugs: see below

Drug causes of gynaecomastia (10-25% of cases)

Relatively Common causes

- **spironolactone (most common drug cause)**
- cimetidine
- digoxin
- cannabis
- diamorphine
- cyproterone
- finasteride
- gonadorelin analogues e.g. Goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

September 2022 exam: H/O developed excessive amounts of breast tissue bilaterally. Which drug is most likely to be responsible? Goserelin (Zoladex)

Physiological changes during pregnancy – endocrine

pregnancy → ↑ oestradiol & prolactin + ↓ LH/FSH.

Progesterone

- Responsible for pregnancy maintenance
- Produced by the corpus luteum until the 10–12 weeks of gestation, after which it is produced by the fetoplacental unit

Human placental lactogen: a hormone synthesized by syncytiotrophoblasts of the placenta, which promotes the production of insulin-like growth factors.

- Increases insulin levels
- Causes insulin resistance
- Increases serum glucose levels and lipolysis to ensure sufficient glucose supply for the fetus
- Maternal insulin resistance begins in the second trimester and peaks in the third trimester.

Pituitary gland

- Hyperplasia of lactotroph cells in the anterior pituitary → physiological enlargement of the pituitary gland (up to 40% increase from pregestational volume)

Thyroid gland

- **Thyroid gland hypertrophy**
  - ⇨ The thyroid gland needs to produce 50% more thyroid hormone during pregnancy to maintain an euthyroid state.
  - ⇨ A 10–20% increase in thyroid mass occurs.
- **Increase in thyroid-binding globulin and albumin due to increased hepatic synthesis.**
  - ⇨ **Pregnancy → ↑↑ thyroxine-binding globulin (TBG) → ↑↑ total thyroxine but does not affect the free thyroxine level**
- **Increase in total T3 and T4**
  - ⇨ **in normal pregnancy (T_3) and T_4 levels show a slight increase with suppressed (TSH) in the first trimester due to the partial thyroid-stimulating action of human chorionic gonadotrophin (beta-HCG).**
  - ⇨ **Free T3 and T4 remains within normal ranges**
- **β-hCG-mediated hyperthyroidism (↓TSH)**
  - ⇨ β-hCG molecule has a similar structure to that of the TSH molecule. β-hCG binds to TSH receptors of the thyroid gland → thyroid stimulation → hyperthyroidism
- **Factors influence thyroid function tests in the pregnant patient.**
  - ⇨ **thyroid stimulatory effects of hCG.**
    - HCG → activation of the TSH receptor → **transient gestational hyperthyroidism.**
    - HCG levels will fall in second and third trimester

Lipids

- ↑ Triglycerides and cholesterol (due to increased lipolysis and fat utilization)

↑ SHBG (Sex hormone-binding globulin) and corticosteroid-binding globulin

Beta-HCG has a degree of thyroid stimulating activity →↓↓ TSH. No intervention is needed

Physiological effects of LH, FSH, and sex hormones

- ♀ **Ovaries**
  - **FSH** → follicular maturation → ↑ **estrogen**
  - **LH** → ↑ estrogen, **ovulation**, and ↑ **progesterone**
- ♂ **Testicles**
  - **FSH** → production of sperm, ↑ **inhibin**
  - **LH** → stimulation of Leydig cells → ↑ **production of testosterone**

In Females:

- **Luteinizing Hormone (LH):**
  - **Function:** Triggers ovulation and the formation of the corpus luteum.
  - **Effects:**
    - Induces the release of an oocyte from the dominant follicle.
    - Stimulates the corpus luteum to produce progesterone, which prepares the endometrium for potential implantation.
- **Follicle-Stimulating Hormone (FSH):**
  - **Function:** Promotes the growth and maturation of ovarian follicles.
  - **Effects:**
    - Stimulates granulosa cells to produce estrogen.
    - Supports the development of the dominant follicle leading up to ovulation.
- **Estrogen:**
  - **Source:** Produced by granulosa cells of the ovaries.
  - **Effects:**
    - Regulates the menstrual cycle by promoting the proliferation of the endometrial lining.
    - Develops and maintains secondary sexual characteristics, such as breast development and the distribution of body fat.
    - Supports bone health and cardiovascular function.
- **Progesterone:**
  - **Source:** Secreted by the corpus luteum post-ovulation.
  - **Effects:**
    - Prepares the endometrium for implantation of a fertilized egg.
    - Maintains pregnancy by inhibiting uterine contractions.
    - Modulates the immune response to support fetal tolerance.

In Males:

- **Luteinizing Hormone (LH):**
  - **Function:** Stimulates Leydig cells in the testes to produce testosterone.
  - **Effects of Testosterone:**
    - Promotes spermatogenesis.
    - Develops and maintains secondary sexual characteristics, such as increased muscle mass, deepening of the voice, and growth of facial and body hair.
    - Supports libido and overall sexual function.
- **Follicle-Stimulating Hormone (FSH):**
  - **Function:** Acts on Sertoli cells within the seminiferous tubules.
  - **Effects:**
    - Facilitates spermatogenesis by nourishing developing sperm cells.
    - Stimulates the production of androgen-binding protein, which maintains high testosterone levels in the testes, essential for sperm maturation.

Dihydrotestosterone (DHT)

Dihydrotestosterone (DHT): Clinical Overview

Biochemistry and Synthesis:

- **Origin:** DHT is synthesized from testosterone via the action of the enzyme 5α-reductase, predominantly in tissues such as the prostate, skin, and liver.
- **Potency:** DHT exhibits greater androgenic activity than testosterone due to its higher affinity for androgen receptors.

Physiological Roles:

- **Fetal Development:** Essential for the differentiation of male external genitalia, including the penis, scrotum, and prostate gland.
- **Puberty:** Facilitates the development of secondary sexual characteristics, such as increased muscle mass, deepening of the voice, and growth of facial and body hair.
- **Adulthood:** Influences prostate growth, sebaceous gland activity, and is implicated in male pattern baldness.

Clinical Implications:

- **Benign Prostatic Hyperplasia (BPH):** Elevated DHT levels contribute to prostate enlargement, leading to urinary symptoms.
- **Androgenetic Alopecia:** DHT plays a central role in hair follicle miniaturization, resulting in male pattern baldness.
- **Prostate Cancer:** While DHT is involved in prostate growth, its direct role in prostate cancer development remains under investigation.

Therapeutic Interventions:

- **5α-Reductase Inhibitors:** Medications such as finasteride and dutasteride inhibit the conversion of testosterone to DHT, effectively reducing DHT levels. These agents are utilized in the management of BPH and androgenetic alopecia.
- **Adverse Effects:** Potential side effects include decreased libido, erectile dysfunction, and gynecomastia.

Diagnostic Considerations:

- **Serum DHT Measurement:** While not routinely performed, DHT levels can be assessed in specific clinical scenarios to evaluate androgen status.
- **Interpretation:** Elevated DHT levels may indicate conditions such as BPH or androgenetic alopecia, whereas low levels could suggest 5α-reductase deficiency.

Comparison of Dihydrotestosterone (DHT) and Testosterone

Aspect	Testosterone	Dihydrotestosterone (DHT)
Chemical Structure	Steroid hormone; can be aromatized to estradiol.	Derived from testosterone via 5α-reductase; cannot be converted to estrogen.
Production	Synthesized primarily in the testes; regulated by luteinizing hormone (LH).	Produced from testosterone in tissues like the prostate, skin, and liver.
Binding	Binds to androgen receptors; circulates bound to sex hormone-binding globulin (SHBG).	Binds to androgen receptors with higher affinity than testosterone.
Potency	Standard androgenic activity.	Approximately 2.5 to 10 times more potent than testosterone in androgenic effects.
Physiological Roles	- Development of male reproductive tissues. - Maintenance of muscle mass and bone density. - Regulation of libido.	- Differentiation of male external genitalia during fetal development. - Development of secondary sexual characteristics during puberty. - Involvement in conditions like benign prostatic hyperplasia and androgenetic alopecia.
Clinical Implications	Deficiency can lead to hypogonadism; excess may cause polycythemia and cardiovascular issues.	Elevated levels associated with prostate enlargement and male pattern baldness; deficiency can result in underdeveloped male genitalia.

Composition

- Testosterone is a steroid hormone and can be converted to oestradiol.

Production

- **LH** → stimulates testosterone production
- **FSH** → spermatogenesis

Binding

- It binds to intracellular receptors and is mostly bound to sex-hormone binding globulin (SHBG)

Conversion

- Testosterone converted to dihydrotestosterone (**DHT**) in the body by the enzyme **5α-reductase**. DHT is a more active compound than testosterone.
- The absence of **5α-reductase** or the absence of **DHT receptors** leads to testicular feminisation.

Function

- During fetal development and early life: differentiation of the penis, scrotum, and prostate.
- expression of male secondary sex characteristics
- During late adulthood: prostate growth, male pattern baldness, and sebaceous gland activity.

Deficiency

- **→↓ testosterone is due to either:**
  - ⇨ ↓ free level due to ↓ production (Leydig and pituitary dysfunction) (Lead to ↑ synthesis of SHBG)
    - increasing age: total testosterone concentrations fall slightly, and free testosterone fall more.
  - ⇨ ↓ activity at receptor often due to androgen receptor deficiency (5α-reductase deficiency).
  - ⇨ Patients with 5α-reductase deficiency will have ambiguous genitalia at birth until they reach puberty, when the testosterone surge causes growth of external male genitalia, however, these patients are otherwise healthy. Individuals with this deficiency sometimes change their gender role in adolescence.
    - **obesity** (hyperinsulinaemia of obesity → ↓SHBG levels → ↓testosterone (*low SHBG* and *normal free testosterone*)

Evaluation

- Initial evaluation: serum testosterone in the early morning, fasting.
- Testosterone levels vary according to the degree of binding to albumin and SHBG; (↑SHBG →↑total testosterone - when testosterone production is low-).
- The equilibrium dialysis method is most useful for measurement of free testosterone (not bound to protein)
- If the testosterone is low:
  - ⇨ measurement of **LH** and **FSH** to determine if the hypogonadism is primary or secondary. If secondary → assessment of other pituitary hormones.
  - ⇨ If the patient has multiple pituitary hormonal deficiencies and/or if the testosterone is less than 200 ng/dL, we suggest *MRI of the sella*.

Testosterone therapy

- **Indications**
  - ⇨ hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
  - ⇨ Older men (>65 years) with age-related decline in testosterone concentration:
    - routinely prescribing testosterone therapy is not recommended
    - In symptomatic (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone, testosterone therapy may be

offered on an individualized basis after discussion of the potential risks and benefits.

- HIV-infected men with weight loss and low testosterone (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain.

- **Target**
  - ⇨ For patients receiving testosterone enanthate, the testosterone level should be between 400 and 700 ng/dL at about half-way between administrations (one week after injection) which are generally given every two weeks.
- **Which type of testosterone therapy is most likely to result in an increase in dihydrotestosterone level?**
  - ⇨ Dihydrotestosteone levels increase with the use of a testosterone **scrotal patch** due to the high concentration of 5α-reductase in genital skin. Levels may return to normal after discontinuation; however, they often remain elevated.

- **Benefits of testosterone treatment**
  - ⇨ ↑sexual interest and activity, slight improvement in walking, slight improvement in mood, ↑ hemoglobin, and ↑ bone mineral density (BMD).
  - ⇨ No change in energy or cognition is expected.
- **Side effects**
  - ⇨ Erythrocytosis leading to elevated haematocrit
    - Haematocrit should be measured 3-6 months after initiating therapy and yearly thereafter.
    - Guidelines suggest that if haematocrit is increased and no other underlying cause is found, the dose should be down-titrated.
  - ⇨ PSA
    - Androgen replacement therapy is contraindicated in patients with prostate cancer and breast cancer.
    - **Urological consultation is recommended** if:
      - ☞ ↑PSA > 1.4 ng/mL within a 12-month period,
      - ☞ a PSA velocity > 0.4 ng/mL/year using the level after 6 months of testosterone therapy as the reference
      - ☞ abnormality on digital rectal examination, or
      - ☞ an I-PSS score of greater than 19.

Testosterone > 5 (normal range <3 pmol/L): investigate for testosterone secreting tumor

Polycystic ovarian syndrome (PCOS)

Polycystic ovarian syndrome - ovarian cysts are the most consistent feature

Infertility in PCOS - clomifene is superior to metformin

Incidence

- Affects **5–20% of women** of reproductive age.

Aetiology

- Not fully understood.
- Associated with **hyperinsulinaemia** and high levels of **luteinising hormone (LH)**.

Clinical Features

1. **Menstrual Irregularities:** Oligo-/amenorrhoea (70%).
2. **Hyperandrogenism:** Hirsutism, acne (60%).
3. **Obesity:** (35%).
4. **Subfertility/Infertility:** (30%), primarily due to chronic anovulation.
5. **Acanthosis Nigricans:** Indicates insulin resistance.
6. **Psychological Symptoms:** Anxiety, depression.
7. **Clitoromegaly:** Rare, suggests severe hyperandrogenism; **requires exclusion of ovarian/adrenal androgen-secreting tumours.**

Investigations

Test	Findings
Pelvic Ultrasound	>8 follicular cysts <10 mm, increased ovarian stroma (91% sensitivity with transvaginal ultrasound).
FSH & LH	Normal/low FSH, elevated LH (LH:FSH ratio >2:1 or 3:1).
Prolactin	Normal or mildly elevated; levels >1000 mU/L suggest prolactinoma.
Testosterone	Normal/mildly elevated; markedly raised (>5 mU/L) suggests tumour.
Sex Hormone-Binding Globulin (SHBG)	Low (due to insulin resistance and hyperandrogenism).
Androstenedione	Elevated in 80% of cases (most specific lab finding for PCOS).
Impaired Glucose Tolerance	40% have impaired glucose tolerance; 10% develop Type 2 Diabetes Mellitus.
Hyperestrogenism	Peripheral conversion of androgens to estrone → endometrial hyperplasia.

Diagnostic Criteria (Rotterdam Consensus)

Diagnosis requires **two of three** criteria:

1. **Oligo-/anovulation.**
2. **Hyperandrogenism:** Clinical (hirsutism, male pattern alopecia) or biochemical (raised free testosterone/androgen index).
3. **Polycystic ovaries on ultrasound.**

Management

General

- **Weight loss:** First-line treatment; reduces symptoms (e.g., hirsutism) with as little as 5% weight loss.

Hirsutism

1. **Combined Oral Contraceptive (COC): Dianette® (cyproterone acetate)** most effective.
2. **Eflornithine cream:** For resistant cases.
3. **Anti-androgens:** Spironolactone, flutamide, or finasteride.

Infertility

1. **Weight loss:** Initial step.
2. **First-line drug: Clomifene** (anti-oestrogen therapy).
   - Mechanism: Blocks hypothalamic oestrogen receptors → increases FSH secretion.
3. **Second-line drug: Metformin** (alone or with clomifene; improves insulin sensitivity).
4. **Gonadotropins:** For clomifene-resistant cases.

Long-Term Complications

- **Type 2 Diabetes Mellitus.**
- **Endometrial Cancer** (due to hyperestrogenism).
- **Obstructive Sleep Apnoea.**
- **Mental Health Disorders.**

Key MRCP Points

1. **Clomifene** is the most effective first-line treatment for infertility in PCOS.
2. **Mechanism of action of metformin in PCOS:** Increases peripheral insulin sensitivity.
3. Most consistently seen feature: **Ovarian cysts on ultrasound.**

- **Testosterone may be normal or mildly elevated** however, **if markedly raised consider other causes**
  - ⇨ **The appropriate initial biochemical investigation**
  - ⇨ Normal or elevated testosterone, but with a low sex-hormone-binding globulin (SHBG) level, resulting in a high free androgen index.
  - ⇨ **An adrenal or ovarian tumour is most unlikely and one should**

MRCPUK-part-1-May 2022 exam: **H/O infertility with PCOS. Apart from advising her to lose weight, which intervention is most effective in increasing her chances of**

conceiving? Clomifene (if clomifene – the first line - is not an option, metformin – the second line - is the right answer)

September 2018 exam: **Which finding is most consistently seen in polycystic ovarian syndrome?** Ovarian cysts on ultrasound

MRCPUK-part-1-January 2023 exam: **What is the mechanism of action of metformin in PCOS?** Increases peripheral insulin sensitivity

Hirsutism

Hirsutism is often used to describe androgen-dependent hair growth in women
Hypertrichosis used for androgen-independent hair growth

Definition

- Excessive male pattern hair growth in women (e.g., on the chin, above the upper lip, and around the umbilicus)

Causes

- Idiopathic (the most common): normal menstrual cycle, normal serum androgen, , and no identifiable cause hirsutism.
- Polycystic ovarian syndrome is **the most common identifiable causes of hirsutism**
- Excess androgen (10% of cases): hirsutism, acne, menstrual dysfunction, alopecia.
  - ⇨ Cushing's syndrome
  - ⇨ congenital adrenal hyperplasia
  - ⇨ androgen therapy
  - ⇨ obesity: due to peripheral conversion oestrogens to androgens
  - ⇨ androgen secreting ovarian tumour
- Drugs

Assessment of hirsutism

- Mild hirsutism and normal menses → do not require laboratory workup and can be treated empirically.
- Moderate or severe symptoms → early morning **total testosterone** level
  - ⇨ if moderately elevated, it should be followed by a plasma **free testosterone** level.
  - ⇨ A total testosterone level greater than 200 ng per dL (6.94 nmol per L) should prompt evaluation for an androgen-secreting tumor.
- Testing for endocrinopathies and neoplasms, such as polycystic ovary syndrome, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and androgen-secreting tumors.

Management

- Advise weight loss if overweight
- Hair removal (Shaving)
- Pharmacologic measures
  - ⇨ Combined oral contraceptive pills: **first-line pharmacologic treatment**
  - ⇨ Facial hirsutism: topical eflornithine - contraindicated in pregnancy and breast-feeding
  - ⇨ Treatment response should be monitored for at least six months before making adjustment.

Hypertrichosis

Definition

- excessive **hair growth above the normal** for the age, sex and race of an individual, in contrast to **hirsutism**, which is excess hair growth **in women** following a male distribution pattern.

Causes

- Drugs:
  - ⇨ **phenytoin**
  - ⇨ **minoxidil** (antihypertensive vasodilator. also used to treat androgenic alopecia → slows hair loss and promotes hair regrowth)
  - ⇨ **ciclosporin**
  - ⇨ diazoxide
- Congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
- Metabolic disorders
  - ⇨ thyroid dysfunction
  - ⇨ porphyria cutanea tarda
  - ⇨ anorexia nervosa

Treatment

- Hair removal

Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)

Type	Polyglandular syndrome type 1	Polyglandular syndrome type 2 Also called (Schmidt's disease)
inheritance	autosomal recessive caused by mutation of **AIRE1** gene on chromosome **21**	polygenic inheritance linked to HLA DR3/DR4.
Prevalence	Rare	More common
Age of presentation	Usually begins in childhood.	Usually begins in adult (most cases occurring between age 20 and 40 years)
Feature	**Most common** Mucocutaneous candidiasis (100%) (typically first feature as young child) Hypoparathyroidism (90%) Adrenal insufficiency (60%) Less common Other autoimmune diseases gonadal failure Primary hypothyroidism	**Most common** Adrenal insufficiency (100%) (the initial manifestation) Hypothyroidism Type-1 diabetes Less common Other autoimmune diseases Gonadal failure Diabetes insipidus (rare)
Diagnosis	**2 out of 3 needed:** chronic mucocutaneous candidiasis (100%) primary hypoparathyroidism (90%), Addison's disease (60%)	Patients have Addison's disease **plus** either: type 1 diabetes mellitus or autoimmune thyroid disease. **No Hypoparathyroidism**

- **Tryptophan hydroxylase autoantibodies** may be found in autoimmune polyendocrine syndrome associated with an autoimmune malabsorption.

Amenorrhoea

Primary amenorrhoea

- **Definition:** failure to start menses by the age of 16 years
- **Causes**
  - ⇨ Turner's syndrome
  - ⇨ testicular feminisation
  - ⇨ congenital adrenal hyperplasia
  - ⇨ congenital malformations of the genital tract

Secondary amenorrhoea

- **Definition**
  - ⇨ Absence of menses for more than 3 months (in women with previously regular cycles) or 6 months (in women with previously irregular cycles)
- **Causes**
  - ⇨ Pregnancy → most common cause of secondary amenorrhea
  - ⇨ Hypothalamic amenorrhoea (e.g. Stress, **excessive exercise**) → ↓ FSH
    - ▪ **Weight-related amenorrhoea**
    - ⇨ amenorrhoea can even be seen at the lower end of the normal range.
    - ⇨ often seen in ballet dancers, who maintain a **low weight** and undergo periods of extreme physical exercise.
    - ⇨ Gaining body weight to above the 50th centile for height normally results in the restoration of menstruation, but if this cannot be achieved oestrogen replacement might be considered.
  - ⇨ Polycystic ovarian syndrome (PCOS)
  - ⇨ Hyperprolactinaemia
  - ⇨ Premature ovarian failure → ↑ FSH
  - ⇨ Thyrotoxicosis (hypothyroidism may also cause amenorrhoea)
    - ▪ Hypothyroidism (↓ T3/T4 → ↑ TRH → ↑ prolactin → ↓ GnRH → ↓ estrogens)
  - ⇨ Sheehan's syndrome
  - ⇨ Asherman's syndrome (intrauterine adhesions)

Initial investigations

- exclude pregnancy with urinary or serum bHCG
- gonadotrophins: low levels indicate a hypothalamic cause whereas raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
- prolactin
- androgen levels: raised levels may be seen in PCOS
- oestradiol
- thyroid function tests

Primary ovarian failure means that the patient never has a normal menstrual cycle, and has the triad of

1. amenorrhea,
2. hypergonadotropinism,
3. hypoestrogenism.

Primary amenorrhoea

Definition

- Absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics.
- However, at age 13 years, if no menses have occurred and there is a complete absence of secondary sexual characteristics such as breast development, evaluation for primary amenorrhea should also begin.

Causes

- Usually **genetic** or **anatomic** abnormalities
- All causes of secondary amenorrhea

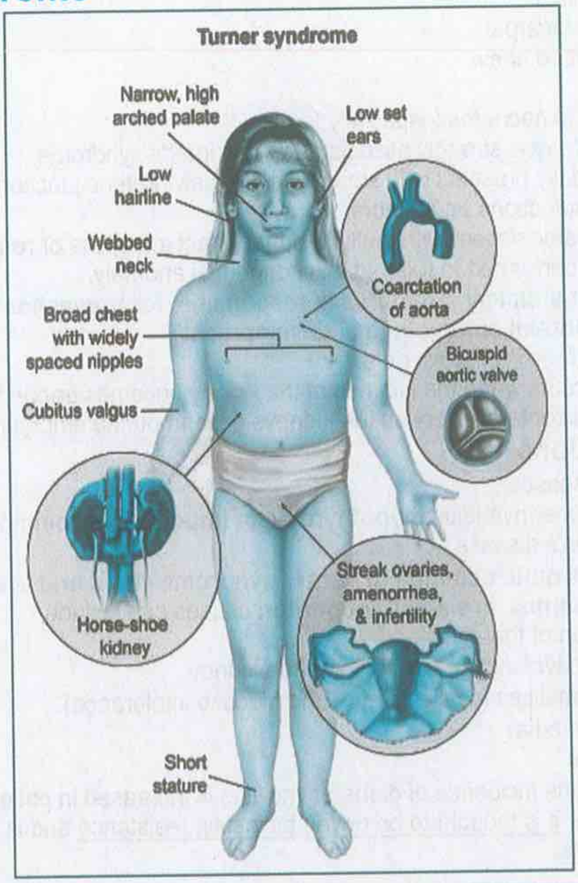
Initial evaluation → **pelvic US** (to determine presence or absence of a uterus)

- **Uterus present** → Initial lab → (FSH, PRL,TSH)
  - ⇨ High FSH → **gonadal dysgenesis**
    - Karyotype should be obtained (46,XY karyotype is associated with a high risk of gonadoblastoma and dysgerminoma, and surgical removal of the gonads is necessary).
  - ⇨ FSH low or normal + low estradiol → **constitutional delay of puberty**, **congenital gonadotropin-releasing hormone (GnRH) deficiency**, or **secondary amenorrhea causes primary amenorrhea**.
- **Uterus absent**
  - ⇨ **Karyotype and total testosterone level** to distinguish between abnormal **müllerian development** (a normal 46,XX karyotype with normal female testosterone level) and **androgen insensitivity syndrome** (46,XY karyotype and normal male testosterone level)

Management

- Correct the underlying pathology (if possible)
- Help the woman to achieve fertility (if desired)
- Prevent complications (eg, estrogen replacement to prevent osteoporosis).

Turner's syndrome



Turner's syndrome - most common cardiac defect is bicuspid aortic valve

Overview

- affects around 1 in 2,500 females.
- caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes.
- **denoted as 45,XO or 45,X**

Features

- short stature
- shield chest, widely spaced nipples
- webbed neck
- cardiac defects:
  - ⇨ **bicuspid aortic valve (15%),**
  - ⇨ coarctation of the aorta (5-10%)
    - hypertension and systolic murmur
- **Primary amenorrhoea**
- **Associated absent uterus and streak ovaries**

- Cystic hygroma (often diagnosed prenatally)
- High-arched palate
- Short fourth metacarpal
- Multiple pigmented naevi
- **Keloid scars**
- Lymphoedema in neonates (especially feet)
- **Horseshoe kidney** is strongly associated with Turner's syndrome
  - ⇨ often initially presents with stone disease, pelviureteric junction (PUJ) obstruction, trauma, infections and tumors.
  - ⇨ In a pediatric patient with multiple urinary tract infections or renal stones, imaging must be performed to rule out this congenital anomaly.
  - ⇨ **Which anatomical structures is responsible for horseshoe kidney anomaly during normal embryological development?**
    - **Inferior mesenteric artery**
    - occurs when the isthmus of the kidney becomes trapped behind the inferior mesenteric artery as the kidneys ascend during embryonic life.

Associated conditions

- Autoimmune diseases:
  - ⇨ autoimmune thyroiditis **(hypothyroidism (much more common in Turner's))**
  - ⇨ and Crohn's disease
- **Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic - essential.** In a **small proportion** causes can include:
  - ⇨ coarctation of the aorta
  - ⇨ and renal dysfunction due to horsehoe kidney.
- Metabolic abnormalities (dyslipidaemia and glucose intolerance)
- Recurrent otitis media.
- Diabetes mellites
  - ⇨ Although the incidence of diabetes mellitus is increased in patients with Turner syndrome, it is thought to be driven by insulin resistance and is very responsive to weight loss.

Diagnosis

- Hypergonadotropic hypogonadism: ↓ estrogen, ↓ androgens, ↑ FSH, ↑ LH
- Karyotype → **identification of 45X0 .**

Management

- **Estrogen and progestogen replacement** → Induction of secondary sexual characteristics
- **Growth hormone replacement** → Attainment of maximum possible final height.
  - ⇨ Given at a dose of 45-50 µg/ kg daily for a period of 3-7 years.
  - ⇨ It is contraindicated if there is the presence of any active malignancy, post-renal transplant for at least one year or if there is evidence of epiphyseal fusion.
  - ⇨ **GH treatment is discontinued on the attainment of final height or if the response is poor** (an increase in growth velocity of less than 50% from baseline) in the first year of treatment.

Prognosis

- **What condition is responsible for most of the excess mortality associated with Turner syndrome?**
  - ⇨ **Thoracic aortic aneurysm rupture**

Premature ovarian failure

The history of prolonged cessation of menses with a normal weight, normal thyroid function tests and a history of coeliac disease is pointed to a diagnosis of premature ovarian failure

Criteria for diagnosis

1. age under 40 years
2. menopausal symptoms (including no or infrequent periods)
3. **and** elevated FSH levels **on 2 blood samples** taken 4–6 weeks apart.

Epidemiology

- occurs in around 1 in 100 women.

Causes

- idiopathic - the most common cause
- chemotherapy
- **autoimmune**
- radiation

Features

- secondary **prolonged amenorrhoea**
- infertility
- climacteric symptoms: hot flushes, night sweats

Investigations

- **raised FSH**, LH levels
- **↓↓oestradiol**
- sex hormone releasing hormones would be elevated in an attempt to drive LH and FSH release.

Treatment

- Hormone replacement therapy (**HRT**) or a combined hormonal contraceptive to protect against osteoporotic fracture.
  - ⇨ HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
  - ⇨ both HRT and combined oral contraceptives offer bone protection
  - ⇨ HRT is not a contraceptive.
- Spontaneous recovery of fertility is unlikely (occurs in only 5%).

Menopause

Definitions

- Peri-menopause → aged over 45, vasomotor symptoms and irregular periods
- menopause → aged over 45, **no** period for at least 12 months, not associated with a pathology and not using hormonal contraception.

Symptoms

- Usually preceded by 4–5 years of abnormal menstrual cycles.
- vasomotor symptoms (e.g. **hot flushes** and sweats): **most common**
- musculoskeletal symptoms (for example, joint and muscle pain)
- effects on mood (e.g. low mood)
- urogenital symptoms (e.g. vaginal dryness)
- Sexual difficulties (e.g. low sexual desire).
- Women with **obesity** tend to suffer from **fewer symptoms** in menopause due to **peripheral conversion of androgens to estrogen** in adipose tissue.
- Most symptoms will disappear spontaneously within 5 years after onset.

Consequences

- ↓↓ bone mineral density → osteoporotic fractures.
- ischaemic heart disease,
- ↓↓ insulin sensitivity
- ↑↑ thrombotic tendency.
- **Increased possibility of developing Alzheimer's dementia**
  - ⇨ Oestrogen deficiency might play a role in the development of dementia.

Investigations

- ↓ estradiol, ↓ progesterone, ↓ inhibin B
- ↑ GnRH, ↑↑ FSH and ↑LH (↑↑FSH is specific for menopause)
- Vaginal pH > 4.5
- Lipid profile: ↑ total cholesterol, ↓ high-density lipoprotein (HDL)
- Testosterone and prolactin levels are within normal ranges (androstenedione is produced by ovarian stromal cells and the adrenal glands.)

Management

- ***Vasomotor symptoms →hormone replacement therapy (HRT)***
  - ⇨ women with a uterus → oestrogen and progestogen
  - ⇨ Women without a uterus →Oestrogen alone.
- **Psychological symptoms** → **low mood or anxiety** → HRT & CBT
  - ⇨ women with low sexual desire → testosterone supplementation if HRT alone is not effective.
- **Urogenital atrophy** → vaginal oestrogen (including those on systemic HRT), also in whom systemic HRT is contraindicated.

The ovaries' failure to produce estrogen **begins in the late 30s** and progresses to the degree that most women have **near-complete loss of estrogen production by their mid-50s.**

Whereas taking estrogen alone increases the risk of endometrial cancer, taking both estrogen and a progestogen in combination, as in most birth control pills, decreases the risk.

All postmenopausal women above the age of 65 should be screened for osteoporosis (i.e., using the DEXA scan to measure bone mineral density).

Hormone replacement therapy (HRT)

Main indication for HRT: control of vasomotor symptoms

HRT: unopposed oestrogen increases risk of endometrial cancer

HRT: adding a progestogen increases the risk of breast cancer

- Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen, combined with a progestogen (in women with a uterus), to help alleviate menopausal symptoms.

Unopposed oestrogen therapy is most appropriate for patient who had a hysterectomy and combined hormone replacement therapy (HRT) is unnecessary.

Indications

- **vasomotor symptoms such as flushing, insomnia and headaches** (The main indication)
- Premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis

Types

- Estrogen therapy: for women who have had a hysterectomy
- Estrogen plus progestin therapy: for women with a uterus

Advantages of hormone replacement therapy (HRT)
1. improvement in menopausal symptoms
2. protection against fractures of the wrist, spine, and hip secondary to osteoporosis.
3. reduce incidence of colorectal cancer
4. reduce incidence of Alzheimer's

- **Hormone replacement therapy and effects on bone mass**
  - ⇨ Reduction in total-body bone mass **begins in women in their late twenties**
  - ⇨ This loss is accelerated at the menopause
  - ⇨ Both trabecular bone loss at the level of the vertebrae and cortical bone loss at the radius are prevented by oestrogen therapy
  - ⇨ The risk of osteoporotic fractures is reduced, but not eliminated, by oestrogen therapy
  - ⇨ If the uterus has been removed in a patient, there is no need for additional progesterone therapy
  - ⇨ **The effect of oestrogens on bone loss may be reduced after 10 years of oestrogen therapy**

Adverse effects

- Cancer
  - ⇨ Unopposed estrogen can result in endometrial hyperplasia → increased risk of endometrial cancer
  - ⇨ Estrogen plus progestin therapy → increased risk of breast cancer
- Thromboembolism: Cardiovascular disease: coronary heart disease, **deep vein thrombosis**, pulmonary embolism, stroke

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

- **Mechanism of action**
  - ⇨ estrogen **antagonist** in **breast** and **endometrium**
  - ⇨ **agonist** in bone to increase mineralisation
- **Clinical use**
  - ⇨ **osteoporosis in menopausal women**
  - ⇨ breast cancer prevention in women high risk for breast cancer
- **Toxicity**
  - ⇨ ↑ risk of venous thromboembolism
  - ⇨ induces menopause →hot flashes

Tamoxifen

- **Mechanism of action**
  - ⇨ **mixed oestrogen-receptor antagonist and partial agonist** depending on the target tissue
    - ❖ estrogen **antagonist** in **breast**
    - ❖ estrogen **agonist** in **endometrium** and **bone**
- **Clinical use**
  - ⇨ estrogen and progesterone receptor positive **breast cancer**
  - ⇨ breast cancer prevention in women high risk for breast cancer
- **Toxicity**
  - ⇨ ↑ risk of venous thromboembolism
  - ⇨ ↑ **risk of endometrial cancer** secondary to agonist activity
  - ⇨ induces menopause →hot flashes

Androgen insensitivity syndrome

The testosterone which is in the male range, the history of hernias as a baby and absence of acne or secondary sexual hair are all pointers towards androgen insensitivity syndrome.

The presence of **breast development** in the **absence of secondary sexual hair**, with a history of **hernias** as a child is suggestive of a diagnosis of **androgen insensitivity syndrome**. It is likely that the hernias were related to **undescended testes**. The vagina is blind ended, and there are no ovaries.

Pathophysiology

- **X-linked recessive mutation** of the gene encoding the androgen receptor (AR gene) → Defects in the androgen receptor → end organ insensitivity to androgens. end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype.
- Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- Primary amenorrhoea
- Undescended testes causing groin swellings, Cryptorchidism (absence of one or both testes from the scrotum)
- External genitalia ranges from normal female to female with clitoromegaly, to under-developed male (hypospadias) → **Associated with abdominal hernias.**
- Breast development may occur as a result of **conversion of testosterone to oestradiol**
- Blind-ended vaginal pouch, uterine and fallopian tube agenesis (due to testicular anti-Mullerian hormone secretion)
- Scant or no pubic hair

Diagnosis

- **High level of LH**
- ↑ Oestrogen
- Normal/↑ testosterone levels (no virilization)
- **Buccal smear** or chromosomal analysis to reveal 46XY genotype

Management

- Counselling - raise child as female
- Bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- Oestrogen therapy

Disorders of sex hormones

The table below summarises the findings in patients who have disorders of sex hormones:

Disorder	LH	Testosterone
Primary hypogonadism (Klinefelter's syndrome)	High	Low
Hypogonadotrophic hypogonadism (Kallman's syndrome)	Low	Low
Androgen insensitivity syndrome	High	Normal/high
Testosterone-secreting tumour	Low	High

Menstrual cycle

The menstrual cycle may be divided into the following phases:

	Follicular phase (proliferative phase) (from day 1 until day 14)	**Luteal phase (secretory phase)** (From day 15 until day 28)
Ovarian histology	• A number of follicles develop. • One follicle will become dominant around the mid-follicular phase	• Corpus luteum
Endometrial histology	• Proliferation of endometrium	• Endometrium changes to secretory lining under influence of progesterone
Hormones	• A rise in FSH results in the development of follicles which in turn secrete oestradiol • When the egg has matured, it secretes enough oestradiol to trigger the **acute release of LH. This in turn leads to ovulation** • **Graafian follicle** is a large mature tertiary follicle containing an oocyte that is ready to be ovulated. • Ovulation occurs 14 days before menses, regardless of cycle length. • estradiol stimulates the growth of the endometrium. • Progesterone levels are low • **FSH activates aromatase within granulosa cells, increasing estradiol production.** • The main hormone controlling the follicular phase is estradiol, secreted by Granulosa cells.	• corpus luteum produces (3 hormones) estrogen, inhibin, and progesterone. • **progesterone** is **significantly higher** than in other phases of the menstrual cycle. • If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall
Cervical mucus	• Following menstruation the mucus is thick and forms a plug across the external os • Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit	• Under the influence of progesterone it becomes thick, scant, and tacky

	Follicular phase (proliferative phase) (from day 1 until day 14)	**Luteal phase (secretory phase)** (From day 15 until day 28)
Basal body temperature	• **Falls** prior to ovulation due to the influence of oestradiol	• **Rises** following ovulation in response to higher progesterone levels

Which hormone levels would be most likely to indicate the occurrence of ovulation?
➔ Luteinising hormone

At which point in the menstrual cycle do progesterone levels peak?
➔ Luteal phase
⇨ Progesterone is secreted by the corpus luteum following ovulation.

Which mechanism is most likely responsible for the missed period in early pregnancy?
➔ **Syncytiotrophoblast produces human chorionic gonadotropin (hCG), which stimulates progesterone production by the corpus luteum.**

Delayed puberty

The first visible sign of puberty in males is testicular enlargement, while in females it is breast development.

Definition

- Absent or incomplete development of secondary sex characteristics by the age of 14 years in boys or 13 years in girls

Causes

- **Constitutional delay of growth and puberty (normal variants of growth): the most common cause of delayed puberty**
- **Primary/ hyper**gonadotrophic hypogonadism: e.g. Klinefelter's and Turner's syndromes.
- **Secondary/ hypo**gonadotrophic hypogonadism: causes
  - ⇨ Genetic defects: (e.g., Kallmann syndrome, Prader-Willi syndrome, Gaucher disease)
  - ⇨ Malnutrition (e.g., anorexia nervosa)
  - ⇨ Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis)

Delayed puberty with short stature	**Delayed puberty with normal stature**
Turner's syndrome Prader-Willi syndrome Noonan's syndrome	polycystic ovarian syndrome androgen insensitivity Kallman's syndrome Klinefelter's syndrome

Features

- **Signs of delayed puberty in girls include:**
  - ⇨ Absence of breast development by age 14 years
  - ⇨ Pubic hair absent by age 14
  - ⇨ More than five years between the start and completion of breast growth
  - ⇨ **Menarche has not occurred by age 16.**
- **Signs of delayed puberty in boys include:**
  - ⇨ No testicular enlargement by age 14 years
  - ⇨ Pubic hair absent by age 15
  - ⇨ More than five years between the start and completion of growth of the genitalia.

Diagnosis

- **Primary hypogonadism** → ↓gonadal hormones (testosterone in boys and estradiol in girls) + ↑ luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- **Secondary hypogonadism** → ↓hypothalamic gonadotropin-releasing hormone (GnRH) → low to normal LH and FSH → ↓gonadal hormones
- **Constitutional delay** is usually assessed using a **bone age assessment** (radiography of the hand and wrist) and measuring the patterns of ossification at the epiphyses of the bones of the hands → delayed bone age.

Management

- Constitutional delay: Observation
- Organic delay: Sex-steroid therapy to induce puberty + lifelong hormone replacement therapy after puberty

Gynaecomastia

Definition

- Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an **increased oestrogen: androgen ratio**.

Causes

- It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

• physiological: normal in puberty • syndromes with androgen deficiency: Kallman's, **Klinefelter's (47, XXY karyotype)** • testicular failure: e.g. mumps • liver disease • testicular cancer e.g. **seminoma** secreting hCG	• ectopic tumour secretion • hyperthyroidism • haemodialysis • starvation/refeeding • drugs: see below

Drug causes of gynaecomastia (10-25% of cases)

Relatively Common causes	Very rare drug causes of gynaecomastia
• **Spironolactone (most common drug cause)** • Cimetidine • **Digoxin** • Cannabis • Diamorphine • Cyproterone • Finasteride • Gonadorelin analogues, e.g. Goserelin, buserelin • Oestrogens, anabolic steroids	• Tricyclics • Isoniazid • Calcium channel blockers • Heroin • Busulfan • Methyldopa

Hypogonadism

Primary hypogonadism (Hypergonadotropic hypogonadism)

if LH and FSH are not elevated a primary hypogonadism is excluded.

- **Pathophysiology**
  - ⇨ gonadal insufficiency (↓ testosterone, ↓ estrogen) → ↑ gonadotropin secretion (↑ FSH and ↑ LH) from the anterior pituitary (lack of negative feedback from the impaired gonads)
- **Causes**
  - ⇨ Congenital abnormalities: (Primary gonadal insufficiency):
    - Turner syndrome (females)
    - Klinefelter syndrome (males)
    - androgen insensitivity syndrome
  - ⇨ Acquired diseases: (Secondary gonadal insufficiency) →(damage to leydig cells or ovarian tissue):
    - Medications (Radiation, chemotherapy, Ketoconazole, Glucocorticoids, toxins)
    - Autoimmune disease
    - Infections (**mumps**, tuberculosis)
    - **Tumour, infiltration (Testicular tumour)**
    - Chronic systemic illnesses (eg: Hepatic cirrhosis, Chronic renal failure)
    - Ageing: **Andropause** (↓ **testosterone with age >50).**
    - Primary testicular failure (**idiopathic failure**).
- **Investigations**
  - ⇨ ↑LH & FSH + ↓ testosterone + ↓ sperm count
  - ⇨ **Testicular ultrasound (the most important investigation after blood hormones)**

Secondary hypogonadism (hypogonadotrophic hypogonadism)

In male patients with low libido have been found to have a low testosterone first line investigation should include prolactin and LH to assess for a central cause

- **Pathophysiology**
  - ⇨ ↓ Pituitary gonadotropins (↓ FSH and ↓ LH) → ↓ testosterone and ↓ estrogen
- **Causes**
  - ⇨ Genetic defects: (e.g., **Kallmann syndrome**, Prader-Willi syndrome, Gaucher disease)
  - ⇨ Hypothalamic and/or pituitary lesions due to: Neoplasm (e.g. prolactinoma, craniopharyngioma, astrocytoma)
  - ⇨ Malnutrition (e.g., anorexia nervosa)
  - ⇨ Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis, **diabetes** and obesity.)
- **Investigations**
  - ⇨ serum **testosterone** and **sperm count** are **subnormal** + **normal or reduced LH and FSH**
  - ⇨ **Prolactin level** (↑Prolactin reduces LH and FSH)
  - ⇨ measure of **free testosterone** (as total testosterone can be low due to SHBG being decreased in obesity and with ageing).
  - ⇨ Pituitary MRI : the best image to exclude other pituitary pathology.

Clinical features

- **Delayed puberty**
- Developmental abnormalities with genitalia (undescended testes, hypospadias)
- Infertility (↓ sperm count), impotence, and/or ↓ libido
- Secondary amenorrhea

Treatment

- Treat underlying cause: e.g., surgical excision of tumors, pharmacotherapy for prolactinomas
- Hormone replacement therapy

Feature	Primary Hypogonadism	Secondary Hypogonadism
Definition	Gonadal failure (testes/ovaries) resulting in decreased sex hormones (testosterone/estrogen) and **increased LH and FSH** (due to loss of negative feedback).	Dysfunction of the **hypothalamus or pituitary gland** leading to decreased gonadotropins (LH and FSH), resulting in low sex hormone levels.
Causes	- **Congenital:** Turner syndrome (females), Klinefelter syndrome (males), androgen insensitivity syndrome. - **Acquired:** Radiation, chemotherapy, autoimmune diseases, infections (e.g., mumps), chronic illnesses (e.g., cirrhosis), and aging (andropause).	- **Genetic:** Kallmann syndrome, Prader-Willi syndrome, Gaucher disease. - **Tumors/Lesions:** Prolactinomas, craniopharyngiomas. - **Systemic Diseases:** Hypothyroidism, diabetes, obesity, anorexia.
Clinical Features	- **Delayed puberty** and genital abnormalities (e.g., undescended testes, hypospadias). - **Infertility**, impotence, decreased libido. - **Females:** Amenorrhea.	- **Similar to primary hypogonadism:** Delayed puberty, infertility, and decreased libido. - Associated with symptoms of **underlying systemic diseases** or **pituitary tumors** (e.g., headaches, visual disturbances).
Diagnostic Tests	- **Hormonal Profile:** ↑ LH & FSH, ↓ testosterone/estrogen, ↓ sperm count. - **Imaging:** Testicular ultrasound.	- **Hormonal Profile:** Normal/↓ LH & FSH, ↓ testosterone/estrogen. - **Serum Prolactin:** Elevated if prolactinoma is present. - **Imaging:** Pituitary MRI to detect pituitary lesions.
Management	- **Address underlying causes:** E.g., treat infections or discontinue offending medications. - **Hormone Replacement Therapy (HRT):** Testosterone or estrogen replacement.	- **Treat underlying cause:** Surgery for tumors, pharmacotherapy for prolactinomas. - **HRT:** Testosterone or estrogen replacement if indicated.

Testosterone and LH levels can help distinguish between different causes of abnormal sexual development:

- **↑ testosterone + ↑ LH → defective androgen receptor (androgen insensitivity syndrome)**
- **↑ testosterone + ↓ LH → testosterone-secreting tumour**
- **↓ testosterone + ↑ LH → primary hypogonadism**
- **↓ testosterone and ↓ LH → hypogonadotropic hypogonadism**

Poor ability to concentrate is most consistent with post-pubertal loss of testicular function, whereas (High-pitched voice, Gynecomastia, Disproportionately long arms and legs, Scant pubic and axillary hair) are most consistent with hypogonadism that develops before puberty.

Hypogonadotrophic hypogonadism: management of male infertility

- Gonadotrophins: hCG + FSH/ hMG: Human menopausal Gonadotrophins (hMG), a mixture of FSH and LH derived from the urine of postmenopausal women.
- Monitor serum testosterone and testicular size.
- Once testes are >8mL, semen analysis every 3– 6 months.
- Takes at least 2 years to maximize spermatogenesis.
- Normalization of spermatogenesis in 80– 90% of ♂.
- Once spermatogenesis is induced, it may be maintained by **hCG alone**.

Management of female infertility (Anovulation)

- ***Hypogonadotrophic (WHO class I)***
  - Treat hyperprolactinaemia with dopamine agonists.
  - Address functional (hypothalamic) amenorrhoea with lifestyle changes to gain weight/ reduce exercise.
  - Then may need ovulation induction
- ***Normogonadotrophic (WHO class II)***
  - Usually PCOS; 1st- line treatment is weight loss if obese.
  - Ovulation induction
- ***Hypergonadotrophic (WHO class III)***
  - Ovarian stimulation has poor results if FSH >15IU/ L.
  - Spontaneous pregnancy is still possible in early Primary ovarian insufficiency (POI).
  - Egg donation is only effective treatment in established POI.

Tip to remember

Testosterone and LH levels can help distinguish between different causes of abnormal sexual development:

1- **High testosterone and high LH**: defective androgen receptor (androgen insensitivity syndrome)
2- **High testosterone and low LH**: testosterone-secreting tumor
3- **Low testosterone and high LH**: primary hypogonadism
4- **Low testosterone and low LH:** hypogonadotrophic hypogonadism

Kallman's Syndrome vs Klinefelter's syndrome

Comparison of Kallmann's Syndrome vs. Klinefelter's Syndrome

Feature	Kallmann's Syndrome	Klinefelter's Syndrome
Definition	Hypogonadotropic hypogonadism due to failure of hypothalamic GnRH neurons to migrate during development, often with anosmia.	Primary hypogonadism caused by the presence of an extra X chromosome (47, XXY karyotype).
Pathophysiology	- Defective migration of GnRH neurons and olfactory bulb development. - Low GnRH → Low FSH/LH → Low testosterone.	- Chromosomal aneuploidy (47, XXY). - Seminiferous tubule dysgenesis → low testosterone and high FSH/LH.
Genetics	X-linked (e.g., KAL1 mutation), autosomal dominant, or autosomal recessive inheritance.	Chromosomal nondisjunction leading to 47, XXY karyotype.
Clinical Features	- Delayed or absent puberty. - Anosmia/hyposmia (impaired sense of smell). - Infertility. - Micropenis, cryptorchidism (in some cases). - May have midline defects (e.g., cleft palate).	- Tall stature with long limbs. - Small, firm testes. - Gynecomastia. - Decreased facial/body hair. - Infertility. - Learning difficulties or behavioural issues.
Hormonal Profile	- Low GnRH, FSH, LH, and testosterone.	- Low testosterone. - High FSH and LH (hypergonadotropic hypogonadism).
Complications	- Infertility. - Osteoporosis (if untreated).	- Infertility. - Increased risk of breast cancer, osteoporosis, and metabolic syndrome.
Diagnostic Criteria	- Low serum FSH/LH with low testosterone. - Anosmia confirmed by olfactory testing. - MRI: Absent or hypoplastic olfactory bulbs. - Genetic testing (e.g., KAL1 mutation).	- Karyotype analysis (47, XXY). - Low testosterone with elevated FSH and LH levels. - Testicular biopsy rarely needed.
Treatment	- Testosterone replacement therapy (improves secondary sexual characteristics and bone health). - Fertility treatment with pulsatile GnRH or gonadotropins (hCG/FSH).	- Testosterone replacement therapy (improves secondary sexual characteristics and bone health). - Fertility treatments rarely effective.

Feature	Kallmann's Syndrome	Klinefelter's Syndrome
Findings in Imaging	- MRI: Hypoplastic or absent olfactory bulbs and sulci.	- No specific imaging findings, but may have small testes on ultrasound.
Prognosis	Good with early treatment, but fertility requires specialized intervention.	Lifelong infertility is common, but testosterone therapy improves quality of life.

Key Points for MRCP:

1. **Kallmann's Syndrome** is characterized by anosmia, low FSH/LH, and absent puberty, treatable with GnRH or gonadotropins.
2. **Klinefelter's Syndrome** is a genetic condition with tall stature, gynecomastia, and primary hypogonadism (high FSH/LH).
3. Karyotype testing differentiates Klinefelter's (47, XXY) from other hypogonadal conditions.
4. Testosterone therapy is a cornerstone of treatment for both conditions, improving secondary sexual characteristics and bone health.

> **Kallman's – LH & FSH low – normal**
>
> **Klinefelter's – LH & FSH – raised**

Kallman's syndrome

- **X-linked recessive.**
- 1 in 10,000 males. More common in men. male to female ratio of 4:1.
- ↓Sex hormone levels are low. LH, FSH levels are inappropriately low/normal
- **Infertility:** In male individuals: cryptorchidism (Cryptorchidism is the absence of one or both testes from the scrotum) and low sperm count. In female individuals: primary amenorrhea
- **Anosmia** present in 75% **(Lack sense of smell) due to failure of the olfactory bulb to develop, leading to loss of gonadotropin releasing hormones.**
- Patients are typically of normal or above average height
- **No mental retardation**
- **Diagnostic test → Fluorescent in situ hybridisation (FISH) is currently the best means of a genetic diagnosis**
- **The appearance on cerebral MRI → Absent olfactory bulbs**
- **If fertility is required (For a male who begin a relationship with a woman): stop testosterone replacement , start exogenous gonadotrophins.**
  - ⇨ Pulsed (NOT Continuous) **GnRH treatment** is needed to restore LH and FSH release.
- **If fertility is not required**; **only testosterone** replacement is required.
- **For a woman who wants to start a family: HCG** to drive production of gonadal steroid hormones, **FSH** to drive ovulation, harvesting of eggs, and **IVF**.

Klinefelter's syndrome

- Klinefelter's syndrome **47, XXY karyotype**
- Incidence: between **1 in 500** and 1 in 1000.
- **has no specific genetic pattern of inheritance (chances of inheriting the disorder < 1%)**
- gynaecomastia →↑**incidence of breast cancer** (20 times higher than a normal male).
- ↑↑**LH/FSH** due to testicular failure
  - ⇨ Leydig cell dysfunction → ↓ testosterone → ↑ LH → ↑ estrogen.
  - ⇨ dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH.
- **Low HDL cholesterol**, elevated triglyceride ,normal or increased (LDL)
- ↑ cardiovascular risk due to lipid abnormality.
- ↓libido
- ↓ bone mineral density → ↑ risk of osteoporotic fractures.
- **Diagnosis is by chromosomal analysis**
- **the most appropriate investigation in suspected cases → FSH, LH**
- **Testosterone is the treatment of choice**

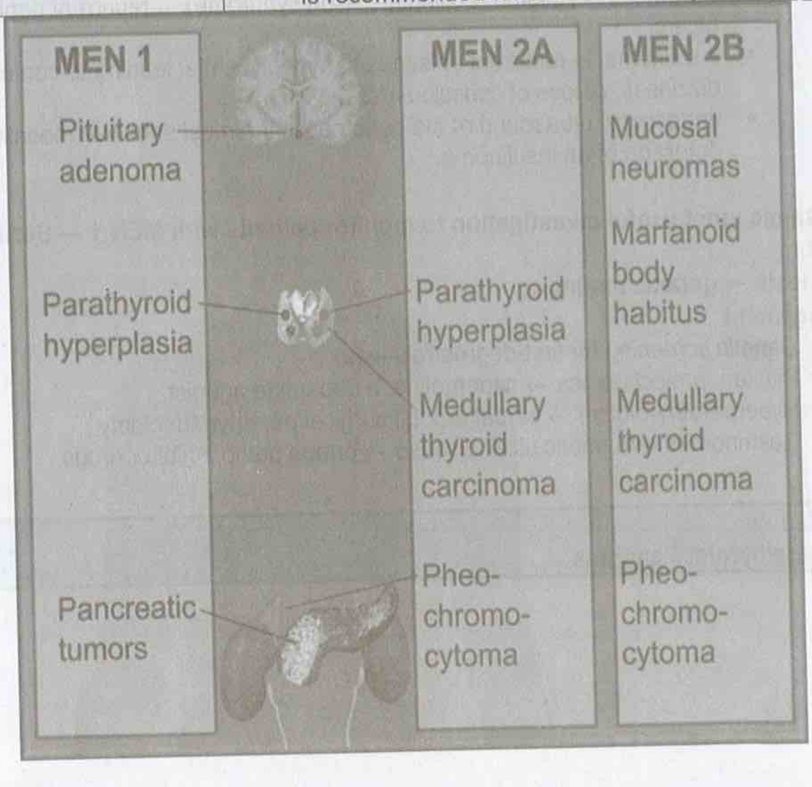
> **Klinefelter's? - do a karyotype**

Multiple endocrine neoplasia (MEN) (Autosomal dominant)

Types

MEN 1	MEN 2A	MEN 2B
3 "P"s ➲ **Parathyroid (90%)** ➲ **Pancreas (60% most commonly** gastrinomas, then insulinoma) ➲ **Pituitary gland**	2 "P"s, 1 "M" ➲ **Parathyroid** ➲ **Pheochromocytoma** ➲ **Medullary thyroid carcinoma**	1 "P", 2 "M"s ➲ **Pheochromocytoma** ➲ **Medullary thyroid carcinoma** ➲ **Marfanoid habitus/Multiple neuromas**
Pathogenesis ➲ **A defect in the gene *MEN1*, a tumor-suppressor gene found on chromosome 11 that codes for menin protein.**	**Pathogenesis** ➲ **A gain-of-function mutations in the gene *RET*. This is a proto-oncogene found on chromosome 10 that codes for a receptor tyrosine kinase.**	

MEN 1	MEN 2A	MEN 2B
Investigations ➲ **the single most useful investigation to monitor is Serum calcium** ➲ **Diagnosis → genetic testing**	**Investigations** ➲ **The most characteristic blood test (↑metanephrines → phaeochromocytoma) & (↑*Calcitonin* → Medullary thyroid cancer)** ➲ **Diagnosis → genetic testing**	
Management ➲ Genetic screening for first-degree relatives ➲ Pituitary prolactinomas → cabergoline, a dopamine agonist ➲ Hyperparathyroidism → partial or total surgical parathyroidectomy ➲ Gastrinomas with peptic ulcer disease → proton pump inhibitor drugs.	**Management** ➲ Genetic screening for first-degree relatives ➲ All first-degree relatives who screen positive for the RET mutation should undergo prophylactic thyroidectomy given the very high risk of medullary thyroid cancer. ➲ For phaeochromocytoma: **alpha blockade with phenoxybenzamine** (Beta blockade without first alpha blocking raises the possibility of rebound hypertension due to unopposed action of the alpha vasoconstrictors) **.Should be removed before other surgical procedures.** ➲ Annual testing of calcium and PTH from the age of 10 is recommended for child with family history of MEN-2	



Multiple endocrine neoplasia

Genetic inheritance

- Autosomal dominant disorder, high penetrance

> **MEN1 & MEN2 gene mutations predominantly occur via autosomal dominant inheritance, however sporadic mutations are also possible.**
> **MEN1 syndrome involves the menin gene mutation.**
> **MEN2 gene mutations involve the RET gene.**

Type 1 multiple endocrine neoplasia (MEN 1)

- **a defect in the gene *MEN1*, a tumor-suppressor gene found on chromosome 11 that codes for menin protein.**
- For MEN1, remember the triad of three Ps, which includes **pituitary**, **parathyroid**, and **pancreatic** tumors.
  - ⇨ Pituitary tumors →↑prolactin → galactorrhea, decreased libido, or infertility.
  - ⇨ Hyperparathyroidism is the most common manifestation in MEN 1 (occurs in 90% of cases) → hypercalcemia → constipation, kidney stones, polyuria, and polydipsia.
  - ⇨ The pancreas is the second most commonly involved organ in MEN 1.
    - **60% of pancreatic endocrine tumours are gastrinomas (most common)** →↑gastrin (Zollinger-Ellison syndrome) → recurrent peptic ulcers.
    - insulinoma → recurrent episodes of hypoglycemia, leading to confusion, dizziness, or loss of consciousness.
    - endoscopic ultrasound of the pancreas is the most sensitive modality for the detection of an insulinoma.

- **The single most useful investigation to monitor patients with MEN 1 → Serum calcium**
- **Diagnosis → genetic testing**
- **Management**
  - ⇨ Genetic screening for first-degree relatives
  - ⇨ Pituitary prolactinomas → cabergoline, a dopamine agonist
  - ⇨ Hyperparathyroidism → partial or total surgical parathyroidectomy
  - ⇨ Gastrinomas with peptic ulcer disease → proton pump inhibitor drugs.

> **MEN1 = three Ps**
> **Pituitary, Parathyroid, Pancreas**

Type 2 multiple endocrine neoplasia (MEN 2)

- **MEN2A and MEN2B are both due to mutations in the gene *RET*. This is a proto-oncogene found on chromosome 10 that codes for a receptor tyrosine kinase.**
- **A gain-of-function mutation in the *RET* proto-oncogene makes it an oncogene, which causes the uncontrolled cell division seen in cancer.**
- **MEN-2 is strongly associated with a family history of unexplained death in childbirth**
- **Subtypes**
  - ⇨ **MEN Type 2a**
    - MEN type 2A includes two Ps and one M—parathyroid tumors and pheochromocytoma, combined with medullary thyroid carcinoma.
    - pheochromocytoma →↑catecholamines such as epinephrine →hypertension and often intermittent episodes of headaches, palpitation, pallor caused by vasoconstriction, and heavy sweating.
    - **Medullary thyroid cancer** often metastasized at presentation →hoarseness
    - **Serum calcitonin** levels should be obtained in the workup for medullary thyroid cancer.
    - **young-onset hypertension with feature of hyperparathyroidism (↑ Ca & ↓ P) → MEN Type 2a**
  - ⇨ **MEN-2b**
    - MEN-2b present earlier than 2a
    - MEN type 2B is associated with a single P and two Ms—pheochromocytoma, medullary thyroid carcinoma, and mucosal neuromas.
    - **Mucosal neuromas** (benign tumors) develop in the mouth, eyes, and submucosa of almost all organs in the first decade of life and appear in 100% of patients with MEN2B (yellowish-white painless nodules on the lips or tongue, sclera, or eyelids).
    - **Marfanoid habitus** → long limbs, wide arm span, and hyperlaxity of joints.

MEN2A = two Ps and one M
Parathyroid, Pheochromocytoma, Medullary thyroid carcinoma

MEN2B = one P and two Ms
Pheochromocytoma, Medullary thyroid carcinoma, Mucosal neuromas

- **Diagnosis → genetic testing**
- **Management**
  - ⇨ Genetic screening for first-degree relatives
  - ⇨ All first-degree relatives who screen positive for the RET mutation should undergo prophylactic thyroidectomy given the very high risk of medullary thyroid cancer.
  - ⇨ For underlying phaeochromocytoma.
    - **full alpha blockade with an agent such as phenoxybenzamine is essential**
    - **the most appropriate additional medication to control blood pressure is → phenoxybenzamine**
    - Beta blockade without first alpha blocking raises the possibility of rebound hypertension due to unopposed action of the alpha vasoconstrictors; as such it is inadvisable to consider bisoprolol or atenolol.
    - **The pheochromocytoma puts the patient at greatest risk, and therefore should be removed before other surgical procedures are performed.**
    - **Annual testing of calcium and PTH from the age of 10 is recommended for child with family history of MEN-2**

Which of the manifestations of MEN-2 has the most malignant potential?
C cell hyperplasia

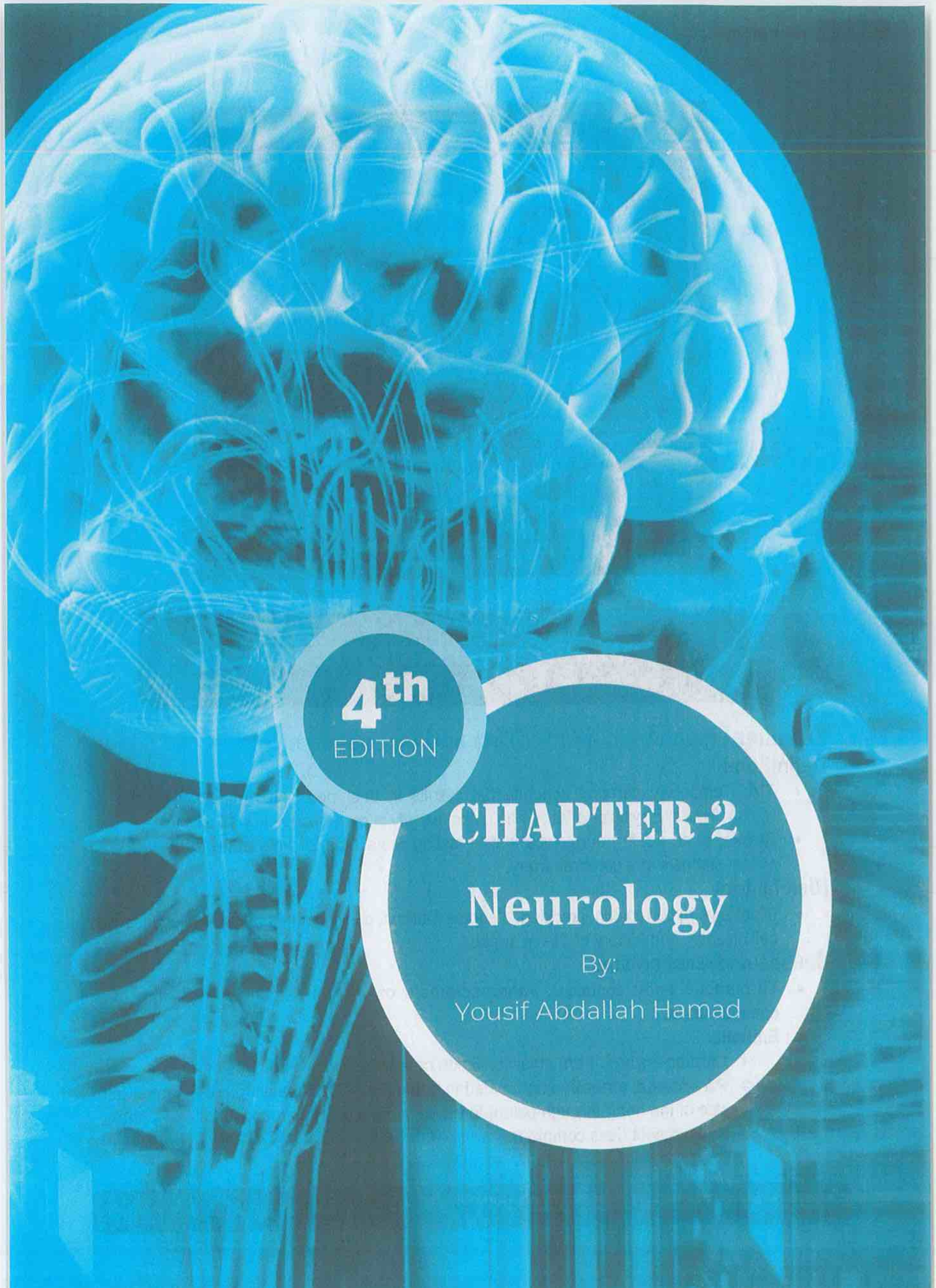
Which finding in a blood test will be the most characteristic in (MEN 2B) patient?
- **Elevated metanephrines → phaeochromocytoma**
- ***Elevated Calcitonin* → Medullary thyroid cancer (used for *screening*, prognosis and *monitoring*)**

Multiple endocrine neoplasia type II is due to mutation in which sort of receptor?
✔ **Membrane-bound tyrosine kinase receptor**

What is the single most useful investigation to monitor patients with MEN 1?
Serum calcium

Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)

Type	Polyglandular syndrome type 1	Polyglandular syndrome type 2 Also called (Schmidt's disease)
Inheritance	Autosomal recessive caused by mutation of AIRE1 gene on chromosome 21	Polygenic inheritance linked to HLA DR3/DR4.
Prevalence	Rare	More common
Age of presentation	Usually begins in childhood.	Usually begins in adult (most cases occurring between age 20 and 40 years)
Feature	**Most common** ➲ Mucocutaneous candidiasis (100%) (typically first feature as young child) ➲ Hypoparathyroidism (90%) ➲ Adrenal insufficiency (60%) **Less common** ➲ Other autoimmune diseases ➲ gonadal failure ➲ Primary hypothyroidism	**Most common** ➲ Adrenal insufficiency (100%) (the initial manifestation) ➲ Hypothyroidism ➲ Type-1 diabetes **Less common** ➲ Other autoimmune diseases ➲ Gonadal failure ➲ Diabetes insipidus (rare)
Diagnosis	**2 out of 3 needed:** ➲ chronic mucocutaneous candidiasis (100%) ➲ primary hypoparathyroidism (90%), ➲ Addison's disease (60%)	➲ Patients have Addison's disease **plus** either: type 1 diabetes mellitus **or** autoimmune thyroid disease. ➲ No Hypoparathyroidism

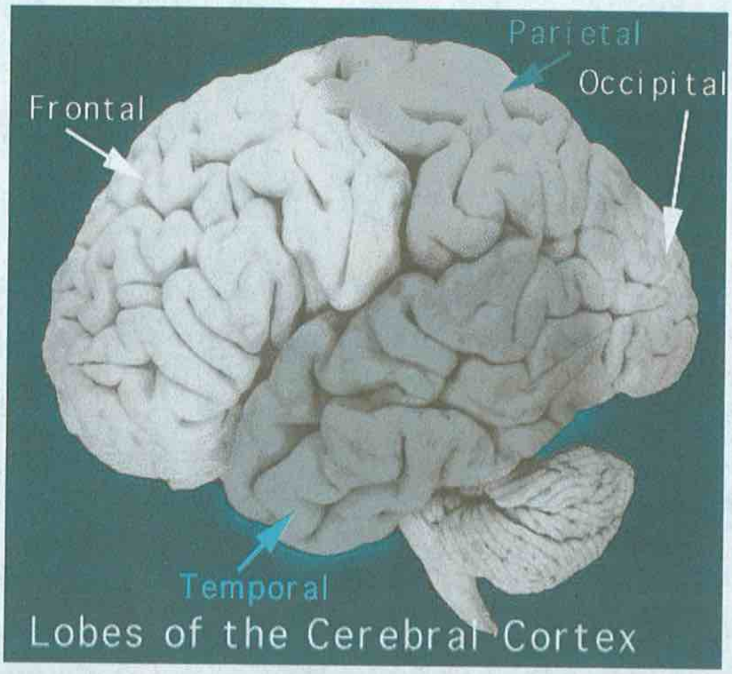


4th EDITION

CHAPTER-2
Neurology

By:

Yousif Abdallah Hamad



Stroke and localisation of lesions

Transient ischaemic attack (TIA) and ischaemic stroke

Definitions

- **TIA:** Temporary cerebral ischemia that results in brief neurologic deficits lasting < 24 hours. Typically, symptoms last < 1 hour (the majority of cases resolve in < 15 minutes).
- **Stroke**: is an acute neurological deficit lasting more than 24 hours due to occlusion or critical stenosis of a cerebral artery.

Risk factors

- Older age, hypertension, smoking, diabetes mellitus, dyslipidaemia, atrial fibrillation, sickle cell disease, and history of TIA or stroke.

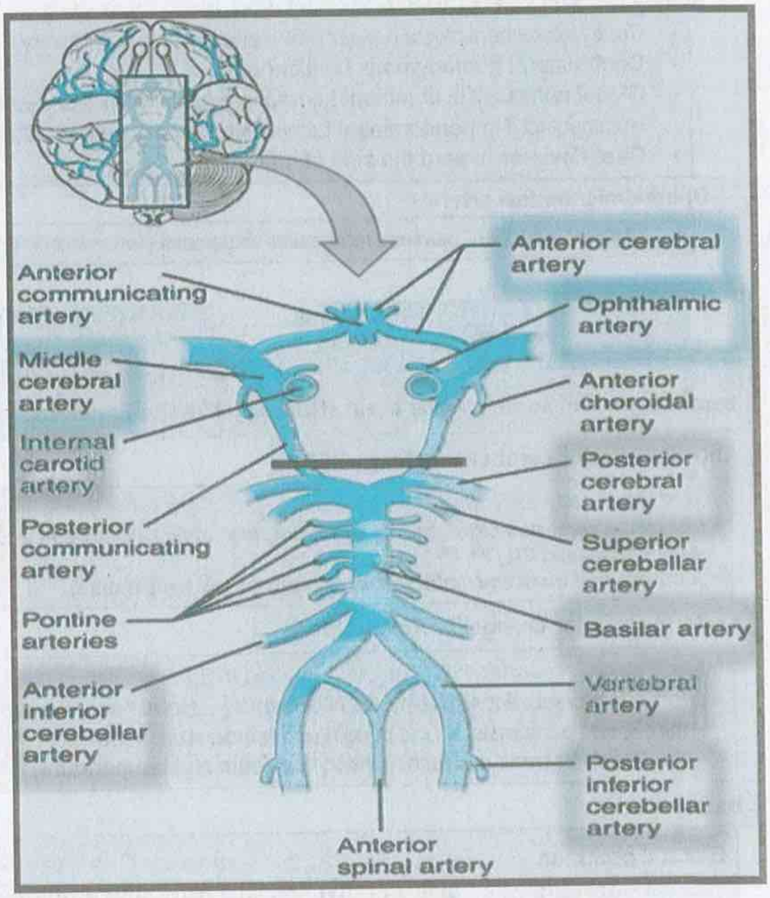
Causes and Mechanisms

- **Thrombotic** (most common): **Atherosclerosis** of internal carotid artery is the most common cause
- **Embolic:**
  - ⇨ **Cardiac emboli:** from atrial fibrillation or left ventricular thrombus or aorta.
  - ⇨ **Paradoxical emboli:** a right-sided thrombus (e.g. DVT) pass from the right-to-left side of the heart through patent foramen ovale (common, found in 20%) or atrial septal defect (less common). **Transoesophageal echocardiography (TOE) is the investigation of choice for diagnosis**.

Features

- **Typical TIA:** Transient monocular blindness (amaurosis fugax), Aphasia or dysarthria, Hemianopia, Hemiparesis and/or hemisensory loss
- **Atypical TIA:** Isolated vertigo, ataxia, diplopia, slurred speech, bilateral decreased vision or unilateral sensory loss involving only one body part.

Affected cerebral vessels and associated features



Stroke by the affected vessel → Anterior circulation

Anterior circulation (from the internal carotid artery) supplies most cerebral hemispheres and deeper brain structures, such as basal ganglia.

Anterior cerebral artery (ACA)

- Contralateral hemiplegia (**lower limbs affected more severely**)
- **Urinary incontinence**

Middle cerebral artery (MCA) (most affected)

- Contralateral hemiplegia (**upper limbs affected more severely**)
- **Contralateral homonymous hemianopia**
- **Global aphasia** if in **dominant** hemisphere (usually left MCA territory)
- Hemineglect if in **nondominant** hemisphere (usually right MCA territory
- **Gaze deviates toward the side of infarction**

Ophthalmic/ Retinal arteries

- Transient, sudden, painless monocular visual loss (**Amaurosis fugax**)

Stroke by the affected vessel → Posterior circulation

Posterior circulation (from vertebral arteries) Supplies brainstem, cerebellum, and some deeper brain structures like the thalamus.

Anterior inferior cerebellar artery (AICA)

Anterior inferior cerebellar artery occlusion → Lateral pontine syndrome

- **Ipsilateral cerebellar signs, horner syndrome, loss of facial sensation to pain and temperature and CN (7th, 8th) palsy**
- ***Contralateral trunk and limbs sensory loss* (pain and temperature)**

Posterior Inferior Cerebellar Artery (PICA)

Lateral medullary syndrome (Wallenberg syndrome):

- ***Ipsilateral cerebellar signs (Ataxia, Nystagmus) & Horner syndrome (ptosis, miosis, and anhidrosis) & Loss of pain and temperature in the face***
- ***Contralateral trunk and limbs sensory loss* (pain and temperature)**

Basilar artery

Bilateral occlusion → bilateral damage to the ventral pons → Locked-in syndrome (quadriplegia + bulbar or pseudobulbar palsy (dysarthria, dysphagia) + preserved consciousness and vertical eye movements and blinking)

Posterior cerebral artery (PCA)

- **Contralateral homonymous hemianopia with macular sparing**
- **Visual (cortical blindness, agnosia, hallucinations)**

Branches of the posterior cerebral artery

Weber's syndrome

- **Ipsilateral CN III palsy**
- **Contralateral weakness**

Diagnostic assessment

- For TIA → ABCD2 score

ABCD2 score (Age, BP, Clinical features, Duration and Diabetes)	
Age	▪ ≥ 60 years (1 point)
Blood pressure	Systolic >140 mmHg and/or diastolic ≥90 mmHg (1 point)
Clinical features	▪ Unilateral weakness (2 points) ▪ Speech impairment but no weakness (1 point)
Duration	▪ 60 minutes or more (2 points) ▪ 10 to 59 minutes (1 point)
Diabetes present	▪ Yes (1 point)
ABCD2 score interpretation ▪ < 4 → low risk ▪ ≥ 4 → moderate to high risk	

- For stroke → ROSIER score (Recognition Of Stroke In the Emergency Room).

ROSIER score (Recognition Of Stroke In the Emergency Room). Exclude hypoglycaemia first	
Assessment	Scoring
Loss of consciousness or syncope	- 1 point
Seizure activity	- 1 point
New, acute onset of:	
▪ asymmetric facial weakness	+ 1 point
▪ asymmetric arm weakness	+ 1 point
▪ asymmetric leg weakness	+ 1 point
▪ speech disturbance	+ 1 point
▪ visual field defect	+ 1 point
Stroke is likely if > 0	

Investigations

- **To confirm the diagnosis:**
  - ⇨ **For TIA:** **Bain MRI** is the first choice, identifies ischemia earlier than CT, determines the territory of ischaemia, and detects alternative pathologies (**CT brain cannot identify early ischemia**)
  - ⇨ **For stroke:** **CT** is **the best initial test** → to rule out hemorrhage (**MRI is the more sensitive**)
- **To identify the cause:**
  - ⇨ **ECG** (e.g AF), and **Echocardiography** (cardioembolic source)

- ⇨ **Duplex ultrasound for carotid stenosis**
- ⇨ **Thrombophilia screening:** if patient is < 50 years old and/or has a history of thrombosis
- ⇨ **Laboratories:** CBC, PT and PTT, serum electrolytes, creatinine, fasting blood glucose or HbA1c, lipids, ESR and CRP

Treatment

- **Immediate treatment: Antiplatelet**
  - ⇨ **Low-risk TIA** (ABCD2 score <4) **or ischaemic stroke** → **Aspirin** 300 mg alone followed by 75 mg daily
  - ⇨ **High-risk TIA** (ABCD2 score of ≥4) → dual antiplatelet therapy (DAPT): aspirin 300 mg plus clopidogrel 300 mg, followed by 75 mg daily for 21 days
- **Secondary prevention**
  - ⇨ **Lifelong antiplatelet: Clopidogrel** is recommended by NICE . **If clopidogrel is not tolerated → Aspirin + dipyridamole lifelong**
  - ⇨ **High-intensity statins** (e.g. atorvastatin 20-80 mg daily) **irrespective of the cholesterol level.**
  - ⇨ **Lifestyle modification** (healthy diet, exercise, stop smoking, reduce alcohol)
  - ⇨ **If there is a carotid stenosis** of **50 to 99%** with TIA or non-disabling stroke → refer urgently for carotid endarterectomy (within two weeks)
    - If the **Duplex ultrasonography** shows stenosis ≥50% → CT or Magnetic resonance **angiography** (**CTA** or **MRA**) helps to define the anatomy **before intervention.**
  - ⇨ **If associated AF** → Anticoagulation started **immediately** in TIA, and **after 14 days in large infarct.**
    - ischaemic stroke + AF → aspirin 300 mg for 2 weeks followed by anticoagulation
    - cerebral infarction in patients with prosthetic valves and who are at significant risk of haemorrhagic transformation →**anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted.**
- **Reperfusion therapy for acute ischemic stroke**
  - ⇨ **Thrombolysis by Alteplase** (a recombinant tissue plasminogen activator, tPA → bind to fibrin in a thrombus (clot) → fibrinolysis) with the **onset of symptoms <4.5 hours**. **Contraindicated if the risk of bleeding is high** (head trauma or surgery in the previous 3 months, Previous intracranial haemorrhage, Intracranial neoplasm, GI malignancy or haemorrhage in the previous 21 days, High BP systolic ≥185 mmHg or diastolic ≥110 mmHg and Hematological bleeding disorders)
  - ⇨ **Mechanical thrombectomy:** whether or not the patient received thrombolytic therapy if the following conditions are met:
    1. haemorrhage excluded by CT or MRI
    2. proximal large artery occlusion in the anterior circulation is the cause of the ischemic stroke, demonstrated by CT angiography (CTA) or MR angiography (MRA)

3. The patient has a persistent, disabling neurologic deficit (eg, a National Institutes of Health Stroke Scale [NIHSS] score ≥6).
4. The patient can start treatment (femoral puncture) within 24 hours of the time last known to be well.

- **Surgical treatment → decompressive hemicraniectomy:** for patients **age 60 years or younger** with infarction involving **>50% of the middle cerebral artery (MCA)** territory associated with a **decreased level of consciousness**, who are thus at high risk of developing malignant edema, if surgery can be initiated within 48 hours of stroke onset.
- **DVT prophylaxis:** subcutaneous heparin or low molecular weight heparin
  - ⇨ ischemic stroke who have restricted mobility and no contraindications → combined VTE prophylaxis: **Intermittent pneumatic compression (IPC)** plus low molecular weight (LMW) heparin.
  - ⇨ For patients treated with thrombolysis→ IPC and VTE prophylaxis should be delayed until 24 hours after thrombolysis.
  - ⇨ TIA or minor stroke on DAPT → withhold pharmacologic VTE prophylaxis
- **Management of hyperglycaemia: Treat with insulin if >11 mmol (target 4- 11)**
- **Management of blood pressure in acute stroke**
  - ⇨ **If thrombolytic therapy is indicated** → BP should be maintained **≤ 185/110** mmHg, before thrombolytic therapy (Labetalol, Nicardipine or Clevidipine are used as first line)
  - ⇨ **If thrombolytic therapy is not indicated:**
    - treat high BP **only if the systolic BP >220** mmHg or **diastolic BP >120** mmHg
    - cautious lowering of BP by approximately 15% during the first 24 hours.
- **Driving advice**
  - ⇨ Single TIA or stroke: must not drive for 1 month
  - ⇨ Multiple TIAs: must not drive for 3 months

Indications decompressive hemicraniectomy in stroke:

- Patient with middle cerebral artery infarction who meet all of the criteria below:
  1. **Age ≤ 60 years**
  2. Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale **(NIHSS) of above 15**.
  3. Decrease in the level of consciousness to give a **score of 1 or more** on item 1a of the **NIHSS.**
  4. Signs on CT of an infarct of at least **50% of the middle cerebral artery** territory

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.

Statins

High intensity (reduce LDL by > 40%)	Medium intensity (reduce LDL by 31% to 40%)	Low intensity (reduce LDL by 20% to 30%)
▪ Atorvastatin 20 – 80 mg ▪ Rosuvastatin 10 – 40 mg	▪ Atorvastatin 10 mg ▪ Rosuvastatin 5 mg ▪ Fluvastatin 80 mg ▪ Simvastatin 20 – 40 mg	▪ Fluvastatin 20 - 40 mg ▪ Pravastatin 10 – 40 mg ▪ Simvastatin 10 mg

Time window for :

- **Thrombolysis (IV Alteplase): < 4.5 hours**
- **Mechanical thrombectomy: < 24 hours**

Carotid endarterectomy for stroke or TIA in the carotid territory only indicated if:

1. ≥50% ipsilateral carotid stenosis
2. The patient not severely disabled

Only glucose test and CT head are required before thrombolytic therapy. Do not delay treatment to complete the diagnostic evaluation.

Vitamin D has a role as a neuroprotective agent towards large artery atherosclerosis. Many patients with ischemic stroke have vitamin D deficiency.

Carotid artery stenosis

Carotid endarterectomy for stroke or TIA in the carotid territory only indicated if:

3. ≥50% ipsilateral carotid stenosis
4. The patient not severely disabled

- Carotid artery stenosis causes 10% to 15% of all ischaemic strokes.
- the annual risk of stroke in patients with asymptomatic carotid disease is between 1% and 2%

Pathophysiology

- Atherosclerotic plaque in the cervical carotid artery is the most common cause.
- Plaque disruption and athero-embolisation into the intracranial circulation is the most common mechanism for stroke.
- The most common site of carotid Atherosclerosis:
  - ⇨ usually at the fork where the common carotid artery divides into the internal and external carotid artery.

Features

- The majority are asymptomatic.
- TIA or stroke
  - ⇨ Plaques rupture → embolism to intracranial arteries → (TIA or stroke) or embolism to retinal arteries → (amaurosis fugax or retinal strokes).
- Cervical bruit

Diagnosis

- Duplex ultrasonography is the preferred initial mode of diagnosis and screening.
  - ⇨ sensitivity of 99%, specificity of 86%
  - ⇨ If the stenosis is less than 50% → no further imaging is needed.
  - ⇨ If the stenosis > 50% → **CTA** or **MRA** for more detailed plaque characterization.
- CT or Magnetic resonance **angiography** (**CTA** or **MRA**) helps to define the anatomy **if intervention is indicated**.

Management

- Initial management → Antiplatelet therapy, Statin and risk factor modification.
- **Carotid revascularization → Endarterectomy**
  - ⇨ Indications:
    - Significant stenosis:
      - ❖ Carotid stenosis > 70% according ECST criteria (European Carotid Surgery Trial' Collaborative Group) or **> 50% according to NASCET** (North American Symptomatic Carotid Endarterectomy Trial) **criteria**.
    - TIA **or** resolving stroke (The patient not severely disabled):
      - ❖ **The benefit of endarterectomy is prevention of future stroke, with dense strokes, if there is no recovery, the benefits are greatly reduced due to end-organ damage.**
      - ❖ **Asymptomatic carotid stenosis ≥ 70% : 1st line → antiplatelet therapy and cardiovascular risk reduction. the best course of action? → Discharge and outpatient follow up**
  - ⇨ Contraindications:
    - 100% carotid stenosis
      - ❖ usually requires a **bypass** procedure, as risk of endarterectomy outweighs benefit.
    - previous stroke with persistent neurological symptoms
  - ⇨ Timing of surgery:
    - should be performed within two weeks. ("urgent" endarterectomy within 2 weeks)
  - ⇨ Benefit:
    - It **reduces the risk of disabling stroke or death by 48%** in a person with severe symptomatic carotid stenosis (>70%) who has had a TIA.

- **Carotid stenting**
  - ➪ used as an alternative to endarterectomy: Indications
    - **Restenosis**.
    - **Previous radiotherapy to the neck** may make endarterectomy difficult, and stenting may be preferred.

Endarterectomy is not recommended in:
- ➲ significant stenosis but asymptomatic side (left carotid in this case)
- ➲ symptomatic side but there is less than 70% (right carotid in his case).

Carotid artery atherosclerosis is an important cause of ipsilateral amaurosis fugax.

Specific stroke syndromes

Midbrain syndromes (Affected vessel : branches of the posterior cerebral artery)

Syndrome	Affected structures	Resulting symptom
Ventral midbrain syndrome (Weber syndrome)	Oculomotor nerve nucleus	Ipsilateral oculomotor nerve palsy
	Corticospinal tract (cerebral peduncle)	Contralateral hemiparesis
Claude syndrome	Oculomotor nerve fibers	Ipsilateral oculomotor nerve palsy
	▪ Superior cerebellar peduncles ▪ Red nucleus	Contralateral ataxia
Paramedian midbrain syndrome (Benedikt syndrome)	Oculomotor nerve fibers	Ipsilateral oculomotor nerve palsy
	Corticospinal tract (cerebral peduncle)	Contralateral hemiparesis
	Red nucleus	Contralateral rubral tremor
Dorsal midbrain syndrome (Parinaud syndrome)	Tectal plate and medial longitudinal fasciculus	▪ Vertical gaze palsy ▪ Eyelid retraction (Collier sign) ▪ Pupillary light-near dissociation (pseudo-Argyll Robertson pupils) ▪ Convergence-retraction nystagmus
Nothnagel syndrome	Superior colliculi	Ipsilateral or bilateral oculomotor palsy
	Superior cerebellar peduncle	Ipsilateral cerebellar ataxia

Weber syndrome
- **ipsilateral III palsy**
- **contralateral weakness**

Pontine syndromes

Syndrome	Affected vessel	Affected structures	Resulting symptom
Ventral pontine syndrome (Millard-Gubler syndrome)	Basilar artery	**Facial** nerve	Ipsilateral facial muscle weakness
		Abducens nerve	Ipsilateral eye abduction palsy
		Pyramidal tracts	Contralateral hemiparesis
Lateral pontine syndrome (Marie-Foix syndrome)	▪ Anterior inferior cerebellar artery (AICA)	Lateral spinothalamic tract	Contralateral loss of pain and temperature sensation
		Middle and inferior cerebellar peduncles	Ipsilateral limb and gait ataxia
		Spinal **trigeminal** nerve nucleus	Ipsilateral loss of facial sensation to pain and temperature
		Facial nerve nuclei	▪ Ipsilateral facial muscle weakness ▪ Ipsilateral decreased lacrimation and salivation ▪ Ipsilateral loss of taste sensation from anterior ⅔ of the tongue
		Vestibulocochlear nerve nuclei	Ipsilateral vertigo, nystagmus, and hearing loss
		Sympathetic fibers	Ipsilateral Horner syndrome
Inferior medial pontine syndrome (Foville syndrome)	Paramedian branches of basilar artery	Pyramidal tracts (corticospinal tract)	Contralateral hemiparesis
		Facial nerve	Ipsilateral facial muscle weakness
		Abducens nerve	Ipsilateral eye abduction palsy and diplopia
		Medial longitudinal fasciculus	Ipsilateral internuclear ophthalmoplegia

Bilateral Ventral Pontine Syndrome (locked-in syndrome)
most commonly caused by infarction of the basilar artery (which supplies the pons) → ischemic **infarction of the ventral pons** → affecting the corticospinal, corticopontine, and corticobulbar tracts → locked-in (quadriplegia with preserved consciousness. patients can communicate by eye movements)

Lateral pontine syndrome VS Lateral medullary syndrome

	Lateral pontine syndrome	Lateral medullary syndrome
Aetiology	**Anterior inferior cerebellar artery (AICA)**	**posterior inferior cerebellar artery (PICA)**
Differences	**Facial nucleus and facial nerve involvement leads to:** • Ipsilateral paralysis of the upper and lower face (lower motor neuron lesion). • Ipsilateral loss of lacrimation and reduced salivation. • Ipsilateral loss of taste from the anterior two-thirds of the tongue. • Hyperacusis.	**Nucleus ambiguous involvement leads to:** Dysphagia, dysarthria, dysphonia
Similarities	**Ipsilateral Horner's syndrome.** Why? **Descending hypothalamic tracts** affected. **Contralateral loss of pain and temperature.** Why? Lateral **spinothalamic tract** affected. **Ipsilateral cerebellar ataxia.** Why? **Cerebellar peduncles** affected. Inferior cerebellar peduncle in medullary and middle cerebellar peduncle in pons. **Nausea, nystagmus, vertigo, vomiting.** Why? **Vestibular nuclei** involved. **Ipsilateral loss of pain and temperature sensation from the face (facial hemianesthesia).** Why? **Spinal trigeminal nucleus** and tract involved. **Ipsilateral hearing loss.** Why? **Cochlear nuclei** and nerve fibers involved.	

Medullary syndromes

Syndrome	Affected structures	Resulting symptom
Medial medullary syndrome (Dejerine syndrome) **Affected vessel:** Paramedian branches of the anterior spinal artery and/or vertebral arteries	Nucleus and fibers of the hypoglossal nerve	Ipsilateral tongue palsy (deviation of the tip to the ipsilateral side)
	Corticospinal tract	Contralateral hemiparesis
	Medial lemniscus	Contralateral decrease in proprioception
Lateral medullary syndrome (Wallenberg syndrome) **Affected vessel:** Posterior inferior cerebellar artery (PICA)	Nucleus ambiguus (CN IX, X, XI)	Ipsilateral bulbar palsy (dysphagia, dysphonia, hiccups, decreased gag reflex)
	Vestibular nuclei	Ipsilateral nystagmus and vertigo
	Lateral spinothalamic tract	Contralateral decrease in pain and temperature sensations in the trunk and limbs
	Spinal trigeminal nucleus	Ipsilateral decrease in pain and temperature sensations in the face
	Inferior cerebellar peduncle	Ipsilateral limb ataxia and dysmetria
	Sympathetic fibers	Ipsilateral Horner syndrome

Lateral medullary syndrome (Wallenberg's syndrome)

Causes: Ischemic occlusion of the **Posterior Inferior Cerebellar Artery (PICA)**, the largest branch of the vertebral artery, supplies the structures of the lateral medulla (vestibular nuclei, spinal cord tracts) and the inferior cerebellar peduncle → **lesion to dorsolateral medulla**	
Ipsilateral	**Contralateral**
• **Cerebellar signs** (Ataxia, dysmetria, dysdiadochokinesia, **nystagmus**) • **Horner syndrome** • **Loss of pain and temperature in the face** (due to 5th CN nucleus damage)	• **Loss of pain and temperature in the trunk and limbs**
Pyramidal tract findings (weakness) are typically absent in lateral medullary lesions.	
Hoarseness (or dysphagia, if present) is fairly specific for lateral medullary syndrome because it points to a lesion of the nucleus ambiguous (cranial nerves IX, X, XI).	

Lateral medullary syndrome:

- **Caused by → Posterior Inferior Cerebellar Artery (PICA) lesion → damage to dorsolateral medulla**
- **Characterised by :**
  - ⇨ **Ipsilateral cerebellar signs (Ataxia, Nystagmus) & Horner syndrome (ptosis, miosis, and anhidrosis).**
  - ⇨ **Contralateral trunk and limbs sensory loss**

Haemorrhagic stroke

Spontaneous Intracerebral haemorrhage (ICH)

Definition: bleeding into the brain by the rupture of a blood vessel. Hemorrhagic stroke may be subdivided into intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).

Causes and pathophysiology

- **Spontaneous (Nontraumatic)**
  - ⇨ **Hypertension:** most common cause of spontaneous ICH. **Putamen (most common site) and thalamus (second most common) for hypertensive intracerebral haemorrhage → non-lobar ICH**
  - ⇨ **Cerebral amyloid angiopathy:** most common cause of spontaneous ICH in individuals > 60 years of age. Deposition of β-amyloid peptides in vessel walls → focal damage with formation of microaneurysms → rupture → **lobar ICH**
  - ⇨ **Arteriovenous malformations:** most common cause of spontaneous intracerebral hemorrhage in children
  - ⇨ **Vasculitis** (e.g., giant cell arteritis)
  - ⇨ **Neoplasms** (e.g., meningioma)
  - ⇨ **Ischemic stroke** (due to reperfusion injury)
  - ⇨ **Coagulopathy** (e.g., hemophilia, anticoagulant use)
  - ⇨ **Stimulant use** (e.g., cocaine and amphetamines; possibly also caffeine)
- **Traumatic brain injury**

Epidemiology: accounts for 15% of strokes (ischaemic stroke ~ 85%)

Features

- Headache
- **Focal neurologic signs and symptoms** may occur, depending on the location and size of the hemorrhage. **Pontine haemorrhage commonly presents with reduced GCS, paralysis and bilateral pin point pupils.**
- **Symptoms of increased ICP** (Nausea and vomiting, Confusion and loss of consciousness. Bradycardia, Fixed pupils)
- Fever is common

Diagnosis:

- Non-contrast head CT(highly sensitive and specific) or MRI (alternative)
- CT angiography for detecting vascular abnormalities

Treatment

- **Stabilisation** of airway, breathing and circulation **(ABCs)**. **Intubation** for airway protection is indicated in patient with **GCS ≤8** or significant respiratory distress.
- **Intensive lowering of systolic blood pressure to <140 mm Hg**
  - ⇨ Intravenous calcium channel blockers (eg, **nicardipine**) and β-blockers (eg, **labetalol**) are the **treatment of choice** for early BP reduction, given their short half-life and ease of titration.
  - ⇨ **During acute phase**, patients may have **resistant HTN due to sympathetic surge**. A few weeks later, they may require fewer medications and be at risk of hypotension unless the doses of medications are adjusted promptly

- **Hyperosmolar therapy** (Mannitol or hypertonic saline)
  - ⇨ **Peri-haematoma oedema** (PHE) develops within the first few days after ICH and may cause elevated ICP, mass effect, midline shift and brain herniation
  - ⇨ **asymptomatic PHE** require **no specific treatment** except maintaining a normal sodium goal → Observe
  - ⇨ symptomatic cerebral oedema and elevated ICP → mannitol and hypertonic saline (HTS) are the first-line
    - Mannitol is an osmotic diuretic. It increases water excretion by the kidneys and reduces cerebral oedema and ICP.
    - HTS **increases plasma osmolarity** and the flow of excess water from cerebral tissue to the blood **via the osmotic gradient**.
    - **hypertonic saline** is slightly **more effective than mannitol** for the treatment of elevated ICP.
  - ⇨ keep serum sodium level at 140–150 mEq/L for 7–10 days to minimise oedema expansion and mass effect.
- **Reversal of coagulopathies**

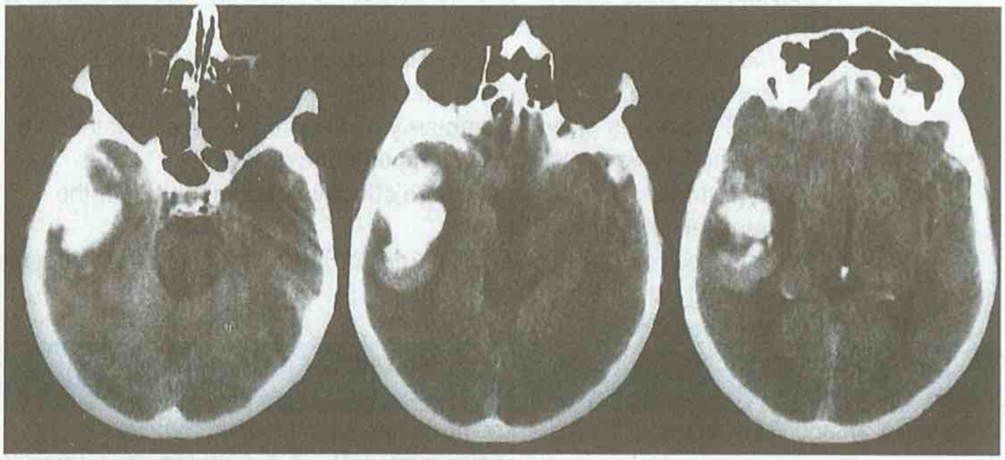
intracerebral haemorrhage in association with	reversed with
Vitamin K antagonist (warfarin)	combination of prothrombin complex concentrates (PCC) and intravenous vitamin K. If not PCC not available → fresh frozen plasma (FFP).
Dabigatran	Idarucizumab
Factor Xa inhibitors (eg, rivaro**xaban**, api**xaban** and edo**xaban**) OR other Direct thrombin inhibitors apart from Dabigatran.	Prothrombin complex concentrate (PCC)
Low-molecular-weight heparin	Protamine
Thrombolytic (eg, recombinant tissue plasminogen activator (rtPA))	1st line → **cryoprecipitate** administration. 2nd line (If cryoprecipitate is contraindicated or unavailable) → tranexamic acid (anti-fibrinolytic agent)

Haemorrhage associated with dabigatran → Idarucizumab

- **Neurosurgery:**
  - ⇨ Patient with a decreased level of consciousness from **intraventricular haemorrhage with hydrocephalus**, mass effect or brainstem herniation should receive ventriculostomy.
  - ⇨ **Hematoma evacuation is recommended in patients with infratentorial hemorrhage who have any of the following:**
    - ⇨ Large hematoma (> 3 cm)
    - ⇨ Declining neurological status
    - ⇨ Hydrocephalus
    - ⇨ Signs of brain herniation (e.g., Cushing triad → increased systolic BP, bradycardia, and irregular breathing)

⇨ **Decompressive craniotomy** in patients with supratentorial hemorrhage and any of the following: Refractory elevated ICP, Large hematoma with a significant midline shift or GCS score ≤ 8.

- **Venous thromboembolism (VTE) prophylaxis** with **intermittent pneumatic compression (IPC)** devices



An intracerebral hematoma is visible in the right temporal lobe.

Subarachnoid haemorrhage (SAH)

Causes

- **Head trauma** is the most common cause of SAH.
- Ruptured cerebral **berry aneurysm** (ballooning arises from a weakened area in the wall of a blood vessel in the brain.) is the most common cause of nontraumatic SAH.
  - ⇨ conditions associated with berry aneurysms include:
    - **adult polycystic kidney disease**,
    - Ehlers-Danlos syndrome and
    - coarctation of the aorta
  - ⇨ occurs most frequently in the anterior half of the circle of Willis.
  - ⇨ The most common site of aneurysm rupture causing SAH is at the junction of the anterior communicating artery and anterior cerebral artery.
- **AV malformations**

Features

- Headache: sudden onset, typically described as the worst headache experienced (thunderclap headache)
- Meningism: neck stiffness, photophobia, nausea and vomiting, meningeal stretch signs (e.g., Kernig's sign and Brudzinski's sign)
- Signs due to mass effect
  - ⇨ Cranial nerve disorders: **Isolated oculomotor palsy indicates aneurysms of the posterior communicating artery.**
  - ⇨ Altered mental status (e.g., (somnolent to comatose))

- ⇨ Focal neurological deficits: See stroke symptoms by affected vessel and stroke symptoms by affected region.
- ⇨ Seizures

Complications

- Rebleeding (in 30%)
- Obstructive hydrocephalus (due to blood in ventricles)
- Vasospasm leading to cerebral ischaemia: **the most common cause of death and disability following aneurysmal SAH → a new focal neurologic deficit following an initial bleed**. Typically, it **starts on day 3 after the initial SAH** and is maximal on days 5-14, resolving on day 21. Treatment includes prophylactic administration of nimodipine and current neurointensive care.
- **Brain stem herniation:** ICH → mass effect and → **brain stem herniation** → false localising signs due to compression of various areas of the brain.
  - ⇨ **uncal herniation**: **3rd CN palsy** (ipsilateral dilated pupil, abnormal external ocular movements, nystagmus) and contralateral hemiparesis (due to compression of the cerebral peduncle.), Ipsilateral hemiparesis and 3rd CN palsy occur late when the lateral translation is so great that it compresses the contralateral third nerve and peduncle.
  - ⇨ **Central herniation**: Bilateral corticospinal tract signs (hypertonia and Babinski signs. Signs of ICP (bradycardia, hypertension, irregular breathing (Cushing response) and a 6th CN palsy (the 6th CN compressed due to its long extracerebral intracranial course). Eye signs (impaired vertical gaze, small pupils, diplopia from either a third or sixth nerve palsy)
  - ⇨ **Treatment:** supportive care with IV mannitol and other hyperosmolar solutions and neurosurgery intervention.

Investigations

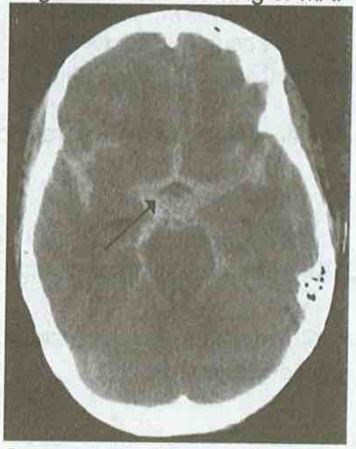
- **Non-contrast CT scan:** the best initial investigation. It is negative in 5%
- **If the history is suggestive, and the CT is normal** → **Lumbar puncture (LP) and CSF examination:**
  - ⇨ **Should be done after 12 hours, allowing time for xanthochromia to develop** (oxidised RBCs → haemoglobin breakdown product)
  - ⇨ **Findings:**
    - elevated opening pressure
    - elevated RBC count that does not diminish from CSF tube 1 to tube 4 differentiates bleeding in SAH from that due to a traumatic spinal tap.
    - **xanthochromia:** detected visually by comparing a vial of CSF with a vial of plain water held side by side against a white background in bright light or by using **spectrophotometry** (detects RBCs breakdown products as they progress from oxyhemoglobin to methemoglobin and finally to bilirubin) which remains <u>positive for 2 weeks</u> with 100% sensitivity.
- CT cerebral angiography: **the best next investigation If the CT image shows SAH** to look for an underlying aneurysm or vascular malformation which may require neurosurgical intervention.
- **ECG: Intracranial hemorrhage ECG changes:**

⇨ Deep, symmetrical T-wave inversion
⇨ Prolonged QT interval

- **If SAH is suspected, obtain a head CT without contrast.**
- **If CT is ⊖, LP is mandatory.**

Management

- **Neurosurgical opinion**
- **ICP management:** elevate head 30°, IV mannitol
- **Prevention of vasospasm and delayed cerebral ischemia:** oral Nimodipine 60 mg every 4 hours for 21 days (only administer nimodipine orally or via enteral tube; Parenteral administration is associated with significant adverse effects (e.g., severe hypotension and cardiac arrest). Nimodipine, a calcium channel blocker (60mg / 4 hourly, if BP allows) → **reduces cerebral vasospasm** (hence maintaining cerebral perfusion) → ↓severity of neurological deficits.
- **Seizure prophylaxis**
- **Blood pressure control:**
  ⇨ If SBP >180 mmHg or mean arterial pressure [MAP] >120 mmHg) → IV labetalol, nicardipine, or clevidipine.
  ⇨ target SBP <160 mmHg or MAP <110 mmHg. Hypotension should be avoided.



Subarachnoid hemorrhage

Cerebral venous thrombosis (CVT)

Epidemiology: more common in young women. Sex: ♀ > ♂, 3:1. Age of onset: ≤ 40 years

Risk factors:

- Prothrombotic (hypercoagulable) conditions: pregnancy and the puerperium, malignancy, obesity, infection, polycythemia.
- Clotting disorders (e.g., factor V Leiden, protein C and S deficiencies, antiphospholipid syndrome),
- Oral contraceptives

Subtypes

- **Superior sagittal sinus thrombosis (SSST) is the most common type of dural venous sinus thrombosis**
- **Cavernous sinus thrombosis (CST)** → 3rd, 4th and ophthalmic (V1) and maxillary (V2) divisions of the 5th cranial nerve affected
- **Superior orbital fissure syndrome:** similar to the cavernous sinus syndrome except for the presence of **proptosis**.
- **Lateral sinus thrombosis** → 6th and 7th cranial nerve palsies

Features

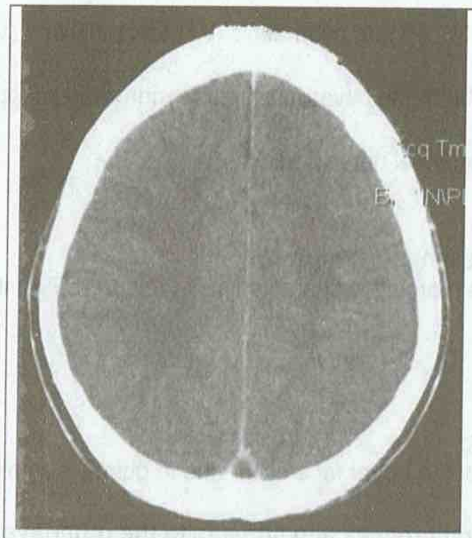
- **Raised intracranial pressure (ICP)**
  - ⇨ **Headache: the most common presenting symptom**
  - ⇨ Nausea & vomiting: Vomiting in the morning is characteristic of raised ICP as it follows a period of lying flat.
  - ⇨ visual disturbance.
  - ⇨ Papilloedema.
- **Peri-orbital oedema**
  - ⇨ may be the **earliest** physical finding
  - ⇨ Chemosis, oedema and cyanosis of the upper face occur due to obstruction of the ophthalmic vein.
  - ⇨ **Eye swelling begins as a unilateral process and spreads to the other eye within 24-48 hours via the intercavernous sinuses**. This is **pathognomonic for cavernous sinus thrombosis (CST)**.
- **Cranial nerve symptoms** (e.g. Ophthalmoplegia): The group of nerves run through the cavernous sinus → III, IV, (V-1, V-2), and VI
  - ⇨ CN VI → Lateral gaze palsy (patient cannot abduct eye) is usually seen first.
  - ⇨ CN III → Ptosis, mydriasis, and eye muscle weakness
  - ⇨ CN V → Hyperaesthesia of the upper face and eye pain
- **Seizures** (focal or generalised)

Investigations

- **D-dimer levels** (the first lab test): An elevated level supports the diagnosis, but a normal D-dimer does not exclude the diagnosis
- **Brain MRI with MR venography (the most sensitive test)**
- **Brain CT with CT venography** (If MR venography is unavailable) → **filling defect** in a vein or sinus and the **reverse delta sign** (empty triangle sign).
- **Evaluation for possible causes** (e.g. CBC, CRP, Thrombophilia screen, antibody studies)

Treatment

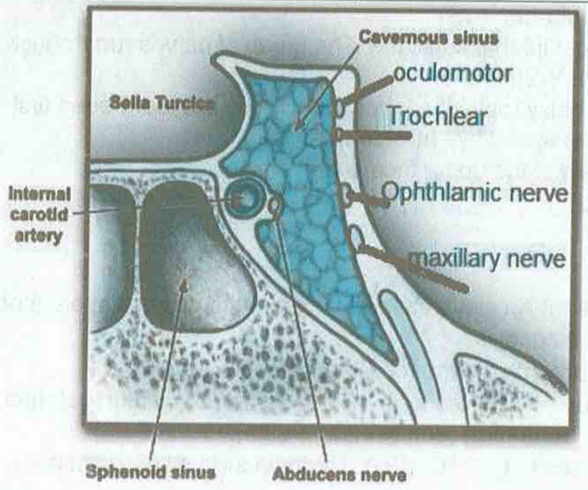
- **Anticoagulants:** low molecular weight heparin (LMWH): Enoxaparin 1 mg/kg SC every 12 hours, followed by warfarin
- **Empiric antibiotic for suspected septic CVT:** Vancomycin PLUS a third- or fourth-generation cephalosporin, e.g., ceftriaxone PLUS metronidazole for anaerobic coverage
- **Dexamethasone** can be used to reduce cerebral oedema.
- **Surgical therapy (e.g. Shunt or clot removal)** indications:
  - ⇨ Progressive neurologic worsening (despite adequate anticoagulation)
  - ⇨ Acute rise in intracranial pressure
  - ⇨ Impending herniation



Empty delta sign indicating a superior sagittal sinus thrombosis

- CT with contrast demonstrating a superior sagittal sinus thrombosis showing the typical empty delta sign.
- Look at the 'bottom' of the scan for the triangular-shaped dural sinus.
- This should normally be white due to it being filled with contrast.
- The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx.
- This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

Cavernous sinus contents



Structures passes through the cavernous sinus:

- **Internal carotid artery**
- **Cranial nerves:**
  - ⇨ **third, fourth, and sixth cranial nerves**
  - ⇨ **Ophthalmic (V1) and maxillary (V2) divisions of the fifth cranial nerve**

The mandibular branch of the trigeminal nerve (V3) does not travel in the cavernous sinus and would therefore not be affected. (NO lower face symptoms)

Which group of nerves run through the cavernous sinus?
→ III, IV, (V-1, V-2), and VI

Cervical vascular dissection

Cervical vascular dissection (Carotid and Vertebral artery dissection)

Causes
- Mechanical forces (eg, trauma, blunt injury, and stretching)
- Arteriopathies (eg, Ehlers-Danlos syndrome, Marfan syndrome and other connective tissue disorders)

Features
- Younger age group <50 years following a recent head or neck injury.
- Pain (headache, neck or facial pain): is the initial common symptom, ipsilateral to the dissected artery.
- TIA or stroke
- Partial Horner syndrome (Ptosis with miosis). anhydrosis is absent because the sympathetic fibres innervating the facial sweat glands are located on the external rather than the internal carotid artery

Diagnosis
- Head and neck angiography (MRA/CTA): the diagnostic modality of choice).

Stroke provoked by minimal trauma (e.g. exercise) is likely due to Cervical vascular dissection until proven otherwise

Triad of carotid dissection:
1. unilateral (ipsilateral) headache
2. **ipsilateral Horner's syndrome** and
3. **contralateral** hemisphere signs (aphasia, neglect, visual disturbance,

Vertebral artery dissection:
- Commonly occurring in young people following a recent head or neck injury.
- severe **occipital headache** and **neck pain** following a **recent head or neck injury**.
- Brainstem Stroke or transient ischaemic attack
- Pain in the ipsilateral neck, face or head.

Localisation of a brain lesion

Brain Lesions and Associated Feature

1. Cortical Lesions

Brain Area (Cortex)	Associated Features
Frontal Lobe	Task sequencing difficulties, Broca's aphasia, disinhibition, personality changes, primitive reflexes, anosmia
Parietal Lobe	Sensory inattention, apraxia, astereognosis, inferior homonymous quadrantanopia, neglect, Gerstmann's syndrome, acalculia
Temporal Lobe	Wernicke's aphasia, superior homonymous quadrantanopia, auditory agnosia, prosopagnosia, memory impairment
Occipital Lobe	Homonymous hemianopia (macula sparing), cortical blindness, visual agnosia, visual illusions, visual hallucinations

2. Subcortical Lesions

Brain Area (Subcortex)	Associated Features
Basal Ganglia	Chorea (caudate damage), Parkinson's disease (substantia nigra), hemiballism (subthalamic nucleus)
Amygdala	Kluver-Bucy syndrome (hypersexuality, hyperorality, hyperphagia, visual agnosia), depression
Hippocampus	Short-term memory impairment (e.g., Alzheimer's disease)

3. Internal Capsule Lesions

Brain Area	Associated Features
Internal Capsule	Pure motor hemiparesis, contralateral weakness and sensory deficits depending on which part is affected (anterior or posterior limb)

4. Thalamic and Hypothalamic Lesions

Brain Area	Associated Features
Thalamus	Contralateral sensory loss, thalamic pain syndrome, memory impairment (medial thalamus)
Hypothalamus	Wernicke-Korsakoff syndrome (involvement of mammillary bodies), endocrine dysfunctions

5. Brainstem Lesions

Brain Area (Brainstem)	Associated Features
Midbrain	Ipsilateral oculomotor nerve palsy, contralateral hemiplegia, fixed midpoint pupils
Pons	Ipsilateral abducens and facial nerve palsy, contralateral hemiplegia, bilateral pinpoint pupils (pontine haemorrhage)
Medulla	Ipsilateral hypoglossal nerve palsy, contralateral body weakness, crossed sensory loss

Crossed neurological signs (ipsilateral motor and sensory cranial nerve signs and contralateral hemiplegia) → localise to the brainstem (midbrain, pons or medulla).

- **Midbrain → (ipsilateral oculomotor nerve palsy , contralateral hemiplegia)**
- **Pons → (ipsilateral abducens and facial nerves palsy, contralateral hemiplegia)**

Stroke and pupils:

- **Midbrain lesions typically cause fixed, midpoint pupils.**
- **Pontine haemorrhage typically cause bilateral pin point pupils**

Visual- spatial awareness deficit

- Due to the Damage to the right parietal lobe
- **Patient unable to navigate around locations, specially places that are new to him , but also familiar locations**

Homonymous quadrantanopias

- PITS (Parietal-Inferior, Temporal-Superior)

Chorea is caused by damage to the basal ganglia, in particular the caudate

Lesions Affecting Brain Nuclei

Nucleus	Functions	Lesion Effects
Caudate Nucleus	- Motor control. - Cognitive processing. - Learning and reward pathways.	- **Motor symptoms**: Chorea, dystonia. - **Cognitive symptoms**: Executive dysfunction, behavioural changes. - **Psychiatric symptoms**: Depression, irritability, psychosis (e.g., Huntington's disease).
Subthalamic Nucleus	- Modulates basal ganglia pathways for motor output.	- **Motor symptoms**: Hemiballismus (sudden, flinging movements of contralateral limbs).
Putamen	- Motor regulation. - Learning processes.	- **Motor symptoms**: Dystonia, rigidity, tremor (e.g., Parkinson's disease). - **Psychiatric symptoms**: Cognitive and mood disorders.
Globus Pallidus	- Modulates voluntary movement.	- **Motor symptoms**: Rigidity, bradykinesia (e.g., Parkinsonism), athetosis (e.g., cerebral palsy). - **Pain and dystonia**: Severe pain, dystonic posturing.
Thalamus	- Sensory relay station. - Motor signal modulation. - Regulates consciousness.	- **Sensory symptoms**: Contralateral sensory loss. - **Motor symptoms**: Coordination deficits. - **Thalamic pain syndrome**: Severe contralateral pain (Dejerine-Roussy syndrome).

Nucleus	Functions	Lesion Effects
Amygdala	- Emotion regulation. - Memory formation.	- **Emotional symptoms**: Emotional blunting, aggression. - **Kluver-Bucy syndrome**: Hyperphagia, hypersexuality, loss of fear.

Pathological Reflexes Indicating Upper Motor Neuron Lesions

Pathological reflexes are abnormal reflex responses that emerge due to **upper motor neuron (UMN) lesions** affecting the **corticospinal tract** or pyramidal system. These reflexes are not present in healthy adults but are seen in conditions such as **stroke, multiple sclerosis, spinal cord injuries**, and **amyotrophic lateral sclerosis (ALS)**.

Key Pathological Reflexes

Reflex	Method of Elicitation	Positive Response	Clinical Significance
Babinski Reflex	Stroking the lateral aspect of the sole from heel to toes.	Upward dorsiflexion of the great toe and fanning of the other toes.	Corticospinal tract dysfunction.
Oppenheim's Sign	Stroking down the anterior medial tibia with pressure.	Dorsiflexion of the great toe and toe fanning.	Alternative to Babinski reflex.
Chaddock's Sign	Stroking the lateral aspect of the foot below the lateral malleolus.	Dorsiflexion of the great toe and toe fanning.	Confirms pyramidal tract lesions.
Gordon's Reflex	Squeezing the calf muscles firmly.	Dorsiflexion of the great toe and toe fanning.	Indicates upper motor neuron lesion.
Schaefer's Sign	Pinching the Achilles tendon.	Dorsiflexion of the great toe and toe fanning.	Upper motor neuron involvement.
Hoffmann's Reflex	Flicking the distal phalanx of the middle finger downward.	Flexion of the thumb and index finger.	Suggests corticospinal tract damage.
Rossolimo's Reflex	Tapping the plantar surface of the toes.	Flexion of the toes.	Seen in pyramidal lesions.
Clonus	Rapid dorsiflexion of the ankle or wrist.	Sustained rhythmic contractions (beats).	Indicates hyperreflexia in UMN lesions.

Cerebellar lesions

Features Indicating Cerebellar Lesions

Feature	Description
Ataxia	Unsteady movements; truncal ataxia for midline (vermis) lesions, gait ataxia for hemispheric lesions.
Dysmetria	Inaccurate control of movement range; overshooting (hypermetria) or undershooting (hypometria).
Dysdiadochokinesia	Impaired ability to perform rapid, alternating movements (e.g., turning hands quickly palm up/down).
Intention Tremor	Tremor that worsens during voluntary movement, most pronounced when nearing a target.
Nystagmus	Involuntary eye movements, often horizontal or vertical
Hypotonia	Reduced muscle tone leading to floppiness and pendular reflexes (limb swings more than usual).
Speech Disturbances	**Scanning speech**: Slow, deliberate speech broken into syllables, indicative of cerebellar dysarthria.

Cerebellar lesion localization:

- **Lesions to the vermis results in → truncal ataxia** and nystagmus.
- **Cerebellar lesions cause neurological deficits on the ipsilateral side**
- **Lesions to the cerebellar hemispheres results in → ipsilateral dysmetria, dysdiadochokinesis, ipsilateral limb ataxia and fast-beat nystagmus towards the lesion.**

Cerebellum lesions: Charcot's neurological triad: scanning speech, nystagmus, and intention tremors

Localisation of speech problems

Aphasia Syndromes

Aphasia	Lesion	Features
Broca's (expressive)	Broca's area (**inferior frontal lobe)** superior division of the left middle cerebral artery (MCA) lesion	Poor fluency and repetition with normal comprehension
Wernicke (receptive)	(**superior temporal lobe)** inferior division of the left MCA lesion	Poor comprehension and repetition with normal fluency
Conduction	**arcuate fasciculus** peri-Sylvian area	poor repetition with normal fluency and comprehension
Transcortical motor	anterior cerebral artery (ACA)-MCA watershed infarct	poor fluency with normal comprehension and repetition
Transcortical sensory	posterior cerebral artery (PCA)-MCA watershed infarct	poor comprehension with normal fluency and repetition
Transcortical mixed	Can be secondary to both an ACA-MCA and PCA-MCA infarct	Poor comprehension and fluency with normal repletion
Global	proximal MCA occlusion affecting both superior and inferior division of the MCA	Poor fluency, comprehension and repetition

Only 1 out of 3 features of speech are affected:

- poor comprehension with normal fluency and repetition → Transcortical sensory aphasia
- poor fluency with normal comprehension and repetition → Transcortical motor aphasia
- poor repetition with normal fluency and comprehension → Conduction aphasia

2 out of 3 features of speech are affected:

- Poor comprehension and fluency with normal repletion →Transcortical mixed aphasia
- Poor comprehension and repetition with normal fluency → Wernicke (receptive) aphasia
- Poor fluency and repetition with normal comprehension →Broca's (expressive) aphasia.

All 3 features of speech are affected:

- Poor fluency, comprehension and repetition → global aphasia

Pupil conditions

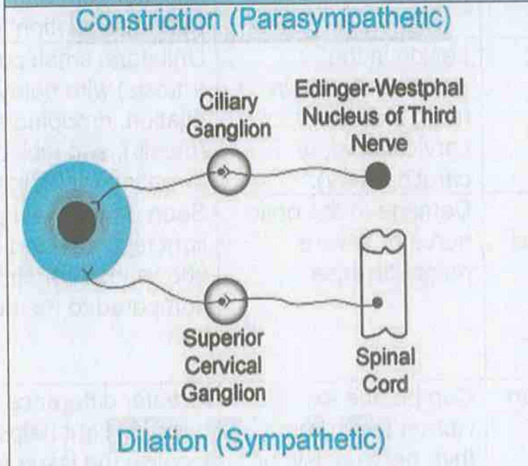
Pupillary control

- **Parasympathetic fibers lead to pupillary constriction (miosis)**
  - ⇨ light enters the eye → retinal ganglion → optic nerve → optic chiasm → optic tract → **pretectal nucleus**→ **Edinger-Westphal nucleus** → ciliary ganglion → pupillary constrictor muscles → causing uniform bilateral miosis
- **Sympathetic fibers lead to pupillary dilation (mydriasis)**
  - ⇨ hypothalamic nuclei → T1 and T2 spinal cord levels → paravertebral sympathetic chain (via the white ramus) → superior cervical ganglion → pupillary dilator muscle
- **Causes of small pupils include:**
  - ⇨ Horner's syndrome
  - ⇨ Old age
  - ⇨ Pontine haemorrhage
  - ⇨ Argyll Robertson pupil
  - ⇨ Drugs, and
  - ⇨ Poisons (opiates, organophosphates).

- **Causes of dilated pupils include:**
  - ➪ Holmes-Adie (myotonic) pupil
  - ➪ Third nerve palsy
  - ➪ Drugs, and
  - ➪ Poisons (atropine, CO, ethylene glycol).

Pupillary control

- **Oculomotor nerve carries parasympathetic efferent to the sphincter pupillae muscle.**
- **Optic nerve carries sympathetic postganglionic fibres to the dilator pupillae muscle.**



Parasympathetic fibres lead to pupillary constriction (miosis)

light enters the eye → optic nerve → optic chiasm → optic tract → **Edinger-Westphal nucleus** → ciliary ganglion → pupillary constrictor muscles → causing uniform bilateral miosis

Sympathetic fibres lead to pupillary dilation (mydriasis)

hypothalamic nuclei → T1 and T2 spinal cord levels → paravertebral sympathetic chain (via the white ramus) → superior cervical ganglion → pupillary dilator muscle

Causes of small pupils (miosis) and dilated pupils (mydriasis)

Causes of small pupils (miosis)	Causes of dilated pupils (mydriasis)
▪ Horner's syndrome ▪ Old age ▪ Pontine haemorrhage ▪ Argyll Robertson pupil ▪ Drugs, and Poisons (opiates, organophosphates).	▪ Holmes-Adie (myotonic) pupil ▪ Third nerve palsy ▪ Drugs, and Poisons (atropine, CO, ethylene glycol).

Pupil Disorders

Disorder	Description	Associated Lesion Site/Condition	Key Features
Tonic Pupil (Holmes-Adie Pupil)	Unilateral dilated pupil with slow or absent light response, but preserved accommodation response (light-near dissociation).	Damage to postganglionic parasympathetic fibres of the ciliary ganglion.	Blurred vision, photophobia, commonly associated with diminished deep tendon reflexes (Holmes-Adie syndrome).
Argyll Robertson Pupil	Small, irregular pupils that constrict with near focus but not to light.	Associated with neurosyphilis and sometimes diabetes mellitus.	Pupils are bilateral, non-reactive to light, but reactive to accommodation ("light-near dissociation").
Horner's Syndrome	Triad of ptosis, miosis, and anhidrosis due to disruption of the sympathetic pathway.	Lesion in the sympathetic chain (e.g., brainstem, cervical cord, or carotid artery).	Unilateral small pupil (miosis) with delayed dilation, drooping eyelid (ptosis), and lack of sweating (anhidrosis).
Marcus Gunn Pupil (Relative Afferent Pupillary Defect)	Abnormal response where the affected pupil dilates instead of constricting during the swinging flashlight test.	Damage to the optic nerve or severe retinal disease.	Seen during swinging light test; affected eye shows less constriction compared to the normal eye.
Anisocoria	Unequal pupil sizes, can be physiologic or pathologic.	Can be due to Horner's syndrome, third nerve palsy, or trauma.	Greater difference in dim or bright light helps localise the issue (e.g., parasympathetic vs. sympathetic dysfunction).
Third Nerve Palsy	Dilated pupil with ptosis and outward deviation of the eye; associated with diplopia.	Lesion in the oculomotor nerve (CN III).	Pupil may be non-reactive to light and accommodation; complete palsy includes ptosis and "down and out" eye position.
Midbrain Lesions	Fixed midpoint pupils with impaired response to light and accommodation.	Lesion in the midbrain, potentially involving the Edinger-Westphal nucleus.	Typically bilateral and associated with other midbrain signs (e.g., vertical gaze palsy).
Pontine Lesions	Bilateral pinpoint pupils due to damage affecting sympathetic innervation.	Pontine haemorrhage or lesions.	Pupils are reactive but very small; often seen with reduced consciousness and quadriparesis.

Key Points for Clinical Assessment

- **Light-Near Dissociation**: Seen in conditions like **Holmes-Adie pupil** and **Argyll Robertson pupil**.
- **Horner's Syndrome**: Confirmed with **cocaine or apraclonidine testing** to assess sympathetic function.
- **Third Nerve Palsy**: Requires urgent evaluation for possible aneurysm if pupil-involving.
- **Marcus Gunn Pupil**: Indicates **optic nerve pathology**, often assessed with the swinging flashlight test.

Clinical Examination of the Pupil: Method, Findings, and Diagnosis

Step/Method	Description	Possible Findings	Associated Diagnosis/Interpretation
1. Inspect Pupil Size and Shape	Observe both pupils for symmetry in size and shape under normal light conditions.	- **Anisocoria** (unequal pupil sizes).	Physiological anisocoria, Horner's syndrome, third nerve palsy, trauma.
		- Irregular pupils.	Argyll Robertson pupil (small, irregular), trauma.
2. Test Direct Light Reflex	Shine a penlight into each pupil individually and observe for constriction.	- **Normal**: Pupils constrict briskly.	Intact optic and oculomotor pathways.
		- **Sluggish or absent constriction**.	Optic nerve damage, third nerve palsy, tonic pupil, pharmacological dilation.
3. Test Consensual Light Reflex	Shine a light into one eye while observing the opposite pupil for constriction.	- **Normal**: Both pupils constrict.	Normal consensual reflex indicates intact interconnection between the eyes.
		- **Absent consensual response** in one eye.	Suggests damage to the optic nerve or severe retinal disease in the non-reacting eye.
4. Swinging Flashlight Test	Rapidly swing the light from one eye to the other, observing the response of both pupils.	- **Marcus Gunn pupil (Relative Afferent Pupillary Defect)**: Dilation of the affected pupil.	Optic nerve damage or severe retinal disease.

Step/Method	Description	Possible Findings	Associated Diagnosis/Interpretation
5. Accommodation Response	Ask the patient to shift focus from a distant object to a near target (e.g., pen held near the nose).	- **Normal**: Pupils constrict as the eyes converge.	Intact parasympathetic pathway and medial rectus function.
		- **Light-near dissociation**: Pupils constrict to accommodation but not to light.	Argyll Robertson pupil (neurosyphilis), tonic pupil (Holmes-Adie).
6. Dim Light Examination	Observe pupil response to darkness or dim light for dilation.	- **Normal**: Pupils dilate equally.	Normal sympathetic pathway.
		- **Delayed dilation** of one pupil.	Horner's syndrome (sympathetic pathway damage).
7. Pharmacological Tests	- **Cocaine Test**: Confirms Horner's syndrome by checking dilation.	- **No dilation** with cocaine in affected eye.	Horner's syndrome.
	- **Pilocarpine Test**: Low-dose pilocarpine induces constriction in tonic pupil but not in normal pupils.	- **Constriction in affected pupil only**.	Confirms tonic pupil (Holmes-Adie pupil).

Common Findings and Their Implications

- **Anisocoria greater in bright light**: Suggests a parasympathetic defect (e.g., third nerve palsy).
- **Anisocoria greater in dim light**: Indicates a sympathetic defect (e.g., Horner's syndrome).
- **Non-reactive, fixed dilated pupil**: May indicate an oculomotor nerve lesion or pharmacological dilation.
- **Small, irregular, non-reactive pupils**: Argyll Robertson pupils associated with neurosyphilis.

Key Points for Clinical Practice

- Always compare pupil responses in both light and dark environments.
- Use a swinging flashlight test to detect subtle afferent defects.
- Pharmacological tests can help confirm specific diagnoses like **Horner's syndrome** or **tonic pupil**.

Argyll Robertson Pupil

Features

- Bilateral small pupils (miosis)
- Accommodation Reflex Present
- Absent pupillary light reflex
- Pupils just like prostitutes, they "accommodate but do not react".

Causes: Neurosyphilis

Ross syndrome

Features: the triad of

1. Anisocoria (unequal pupil size)
2. Loss of deep tendon reflexes and
3. Segmental anhydrosis with a compensatory excessive sweating

Causes: unknown

Adie's tonic pupil (Holmes-Adie syndrome)

Pathophysiology: parasympathetic denervation at the level of the ciliary ganglion and postganglionic nerves.

Features

- Anisocoria (unequal pupil size). Affected eye is dilated usually
- Light-near dissociation pupil (accommodate to near object but do not react to light, slowly constricts in bright light (tonic pupil).
- Absence of deep tendon reflexes

Causes: Idiopathic parasympathetic denervation at the level of the ciliary ganglion and postganglionic nerves.

Anisocoria (unequal pupil size)

↓

light reflex test

constriction of the pupils in response to light

↓

If the light reflex is poor in one eye

↓

slit lamp examination of the eye to rule out intraocular causes

↓

If slit lamp examination is normal, administer low-dose pilocarpine (0.1%) eye drop

↓

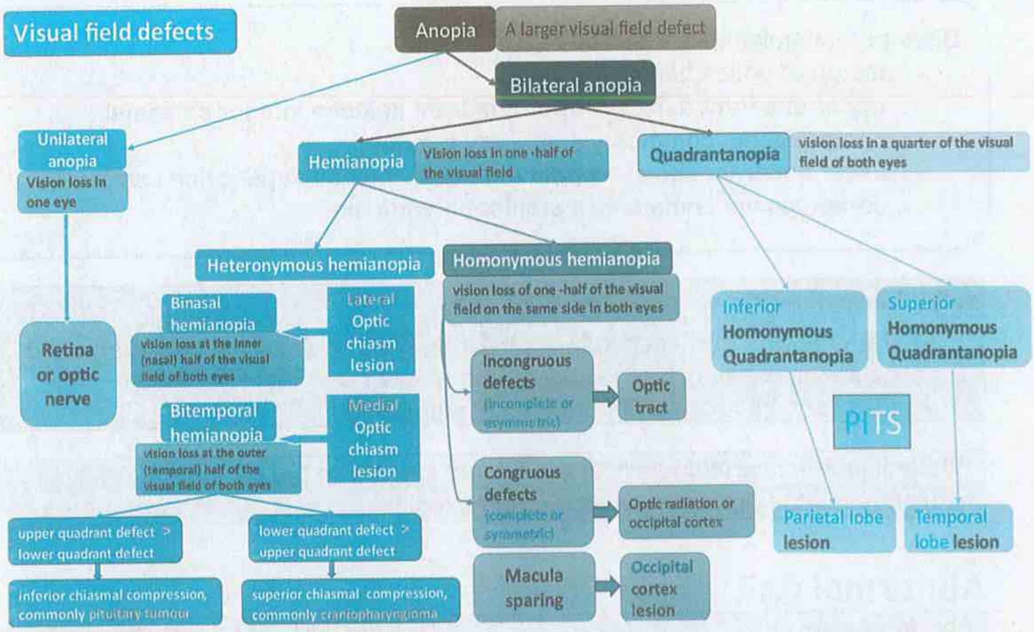
- If pupil constricts: suspect Adie tonic pupil
  - ↓ If pupil constricts: suspect oculomotor nerve palsy
- If pupil does not constrict: administer high-dose pilocarpine (1%) eye drops
  - ↓ If pupil does not constrict: suspect pharmacological mydriasis

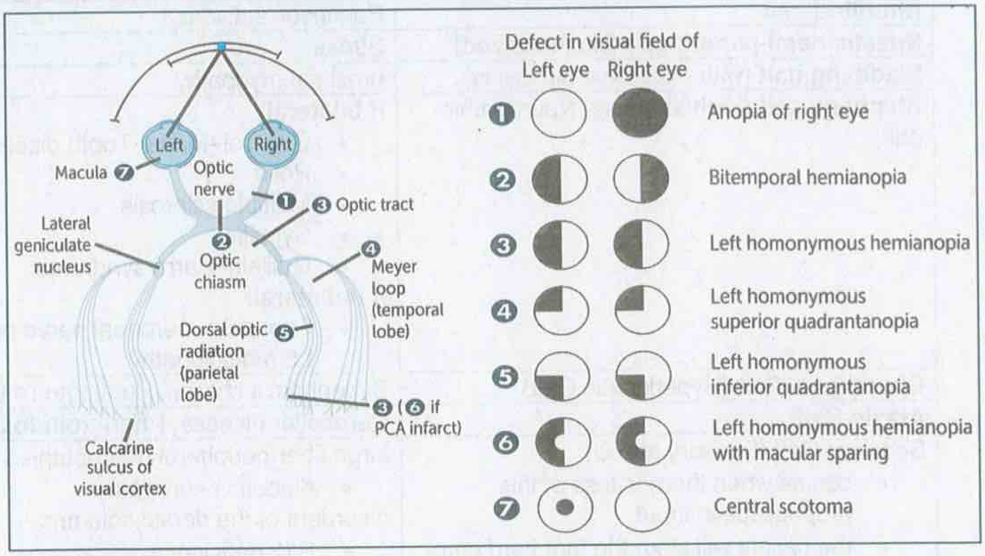
Visual field defects

Type of Visual Field Defect	Description	Associated Lesion Site
Monocular Vision Loss	Loss of vision in one eye.	Lesion anterior to the optic chiasm (e.g., optic nerve).
Bitemporal Hemianopia	Loss of the outer (temporal) half of the visual field in both eyes.	Lesion at the optic chiasm (e.g., pituitary adenoma).
Homonymous Hemianopia	Loss of the same side of the visual field in both eyes (e.g., right or left).	Lesion posterior to the optic chiasm (e.g., optic tract, lateral geniculate body, optic radiations, occipital lobe).
Superior Homonymous Quadrantanopia	Loss of the upper quadrant of the visual field in both eyes.	Lesion in the contralateral temporal lobe (Meyer's loop).
Inferior Homonymous Quadrantanopia	Loss of the lower quadrant of the visual field in both eyes.	Lesion in the contralateral parietal lobe.
Central Scotoma	Loss of vision in the central part of the visual field.	Lesion in the macula or optic nerve (e.g., optic neuritis).
Altitudinal Hemianopia	Loss of the upper or lower half of the visual field in one eye.	Lesion affecting the optic nerve or retinal artery.
Cecocentral Scotoma	Loss of vision affecting the central field and extending to the blind spot.	Lesion involving the optic nerve (e.g., toxic or nutritional optic neuropathy).
Peripheral Field Loss	Loss of vision in the peripheral field.	Lesion in the retina or optic nerve (e.g., retinitis pigmentosa).

Key Points for Localisation

- **Monocular Defects**: Indicate a problem anterior to the optic chiasm (optic nerve or retina).
- **Bitemporal Hemianopia**: Strongly suggestive of an optic chiasm lesion.
- **Homonymous Hemianopia**: Points to a lesion posterior to the optic chiasm (tract, radiation, or occipital lobe).
- **Quadrantanopias**:
  - **Superior ("Pie in the Sky")**: Temporal lobe (Meyer's loop).
  - **Inferior ("Pie on the Floor")**: Parietal lobe.
- **Central and Cecocentral Scotomas**: Often indicate optic nerve pathology.





Visual field defects

Visual field defects:

- **left homonymous hemianopia means visual field defect to the left, i.e. lesion of right optic tract**
- **homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)**
- **incongruous defects = optic tract lesion; congruous defects= optic radiation lesion or occipital cortex**

Bitemporal hemianopia:

- **lesion of optic chiasm**
- **upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour**
- **lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma**

Cortical blindness

- **Patients with cortical blindness frequently have visual hallucinations and occasionally deny that they are blind.**
- **Pupillary reactions and fundoscopy are normal.**

Bilateral internal carotid artery displacement can cause binasal incongruous hemianopia if the optic nerves are compressed.

Abnormal gait

Abnormal gait	Diagnosis
Shuffling gait	Parkinson's disease
Spastic hemi-paretic gait (circumducted)	Stroke
Waddling gait (with excessive hip swing)	proximal myopathy
Steppage gait (High stepping, Neuropathic gait)	**If bilateral:** • Charcot–Marie–Tooth disease • Polio • Multiple sclerosis • Syphilis • Guillain–Barré syndrome **If unilateral:** • Foot drop: peroneal nerve palsy and L5 radiculopathy.
Choreiform Gait (Hyperkinetic Gait)	Sydenham's chorea, Huntington's Disease
Ataxic Gait	Cerebellar disease, **Phenytoin toxicity**
Sensory Gait (Sensory ataxia) • occurs when there is loss of this proprioceptive input • the patient will slam the foot hard onto the ground in order to sense it. • **distinguished from cerebellar ataxia by positive Romberg's sign (normal coordination when the movement is visually observed by the patient, and worsened when the eyes are closed)**	large fiber peripheral neuropathies • diabetic neuropathy disorders of the dorsal columns: • B12 deficiency, • tabes dorsalis

Lesions of cerebellar vermis cause → truncal ataxia and tendency to fall backwards.

Phenytoin toxicity → broad-based ataxic gait

Sensory ataxia is distinguished from cerebellar ataxia by positive Romberg's sign (normal coordination when the movement is visually observed by the patient, and worsened when the eyes are closed)

Spinocerebellar ataxia (SCA):
- **autosomal dominant**
- **should be suspected in patients with progressive loss of coordination, unsteady gait and overall weakness.**

Nystagmus

Definition

- involuntary oscillations of the eyes.

Relation to directions of the gaze

- **constant direction regardless of the direction of gaze**, suggests → a labyrinthine or cerebellar lesion.
- **changes with the direction of gaze** suggests widespread central involvement of **vestibular nuclei.**
- **presents only on lateral gaze → lesion of the brain stem or cerebellum.**
- Nystagmus restricted to the **abducting eye** on **lateral gaze** (ataxic nystagmus) is due to a **lesion of the medial longitudinal bundle** between the pons and mid-brain as in multiple sclerosis (MS).

Causes

- Visual disturbances
- Lesions of the labyrinth
- Central vestibular connections, Brain stem or cerebellar lesions
- Wernicke's encephalopathy
- Nystagmus confined to one eye suggests:
  - ⇨ a peripheral lesion of the nerve or muscle,
  - ⇨ or a lesion of the medial longitudinal bundle.

Vertical VS horizontal nystagmus

- Vertical nystagmus:
  - ⇨ Upbeat nystagmus (occurring on upward gaze: due to a **lesion in the mid-brain**
  - ⇨ **Downbeat nystagmus (fast phase downwards) suggests a lesion in the lower part of the medulla. It is therefore typical of the Arnold-Chiari malformation (Chiari type I malformation).**
- Horizontal nystagmus:
  - ⇨ occurs in unilateral disease of the cerebral hemisphere, with the fast phase directed to the side of the lesion.

Type of Nystagmus	Description	Associated Lesion Site/Condition
Horizontal Nystagmus	Rhythmic, involuntary horizontal eye movements.	Commonly associated with vestibular dysfunction or cerebellar lesions.
Vertical Nystagmus	Rhythmic, involuntary up-and-down eye movements.	Indicates brainstem or cerebellar lesions, such as in the midbrain or medulla.
Rotatory (Torsional) Nystagmus	Circular or rotational eye movements.	Often related to vestibular system lesions or brainstem involvement.
Gaze-Evoked Nystagmus	Occurs when eyes are held at an extreme lateral or upward position; not present in primary gaze.	Indicative of cerebellar or brainstem lesions; can also be due to medication effects.
Pendular Nystagmus	Smooth, sinusoidal, back-and-forth eye movements with equal speed in both directions.	Associated with congenital nystagmus, multiple sclerosis, or visual impairment from birth.
Jerk Nystagmus	Fast phase in one direction followed by a slow phase in the opposite direction.	Often associated with vestibular dysfunction or cerebellar lesions.
Rebound Nystagmus	Brief, opposite nystagmus after the eyes return to the primary gaze from an eccentric position.	Suggests cerebellar dysfunction.
Upbeat Nystagmus	Fast phase directed upward.	Often indicates a lesion in the medulla or the cerebellum.
Downbeat Nystagmus	Fast phase directed downward, seen on downward gaze.	Suggestive of lesions at the cervicomedullary junction or in the cerebellum.
Optokinetic Nystagmus	Induced by tracking a moving visual scene (e.g., watching a rotating drum).	Physiological; abnormal responses may indicate parietal lobe lesions or visual pathway issues.

Key Points for Localisation

- **Horizontal and gaze-evoked nystagmus** often point to **cerebellar or vestibular lesions**.
- **Vertical and downbeat nystagmus** are highly indicative of **brainstem or cerebellar pathology**.
- **Pendular nystagmus** is associated with **congenital or acquired conditions** like multiple sclerosis.
- **Rebound and upbeat nystagmus** suggest **cerebellar involvement**.

Upbeat nystagmus → cerebellar vermis lesions
Downbeat nystagmus → foramen magnum lesions (Arnold-Chiari malformation)

Chorea and Hemiballism

Feature	Chorea	Hemiballism
Definition	Involuntary, rapid, irregular, and jerky movements affecting the limbs, face, or trunk.	Involuntary, violent, flinging movements of one side of the body (unilateral).
Pathophysiology	Results from dysfunction in the basal ganglia, particularly the **striatum (caudate nucleus and putamen)**.	Results from a lesion in the **subthalamic nucleus** of the basal ganglia.
Common Causes	- **Huntington's disease** (genetic neurodegenerative disorder) - **Sydenham's chorea** (post-streptococcal autoimmune response) - **Medications** (e.g., antipsychotics, levodopa) - **Metabolic disorders** (e.g., thyrotoxicosis, Wilson's disease)	- **Stroke** (most common cause) involving the subthalamic nucleus - **Trauma** affecting the basal ganglia
Clinical Features	- Irregular, non-repetitive, and non-purposeful movements - Can affect gait, speech, and facial expressions	- Large, flinging, forceful movements typically involving the proximal limbs - Can interfere significantly with daily activities
Associated Conditions	- **Huntington's disease**: Associated with cognitive decline and psychiatric symptoms **- Sydenham's chorea:** Occurs in children, associated with rheumatic fever	- Often seen post-stroke in older adults
Diagnostic Approach	- Clinical examination - Genetic testing for Huntington's disease	- Clinical examination and history of recent stroke or trauma - Imaging (CT/MRI) to identify subthalamic nucleus lesion
Treatment	- **Dopamine-depleting agents** (e.g., tetrabenazine) for symptomatic relief - **Antipsychotics** may be used to control severe symptoms - **Immunomodulatory therapy** for Sydenham's chorea	- **Dopamine antagonists** (e.g., haloperidol) to reduce movements - Treatment of underlying cause (e.g., stroke management)

Key Points

- **Chorea**: Characterised by non-rhythmic, jerky movements due to **striatum dysfunction** (e.g., Huntington's disease).
- **Hemiballism**: Characterised by large, unilateral, flinging movements due to **subthalamic nucleus lesions**, often secondary to a **stroke**.
- **Management**: Involves symptomatic treatment with medications that reduce excessive movement and addressing the underlying cause.

Chorea and hemiballismus

Both are forms of involuntary movement disorders that worsen with activity and decrease with relaxation and sleep.

Chorea: irregular, spontaneous, and nonrepetitive movements (dance-like movements), mostly distal muscles. Sydenham chorea is the most common cause. damage to the caudate nucleus → decreased suppression of involuntary movements

Hemiballismus: sudden, violent, and flinging movements. mostly proximal muscles. Stroke is the most common cause. damage to the subthalamic nucleus → decreased suppression of involuntary movements

Causes

- **Cerebrovascular (e.g, stroke, AV malformation)**
- **Autoimmune or inflammatory (e.g, Sydenham chorea, SLE)**
- **Drugs and toxins (dopaminergic drugs, carbon monoxide, mercury)**
- **CNS infections and tumours**
- **Metabolic or endocrine (e.g, hyperglycemia, hyperthyroidism, hypo/hypercalcemia, renal or hepatic failure, Vitamin B1, B12, niacin deficiency)**

Management: treatment of underlying cause + symptomatic

- **1st line: Dopamine-depleting agents (tetrabenazine): vesicular Monoamine Transporter 2 (VMAT2) Inhibitor**
- **2nd line: atypical neuroleptics: olanzapine, risperidone**

Cranial nerves disorders

Cranial nerves

The major characteristics of the 12 cranial nerves

Cranial Nerve (CN)	Location	Function	Features of Injury
I - Olfactory	Frontal lobe, olfactory bulb/tract	Sense of smell	Anosmia (loss of smell), may be associated with frontal lobe lesions.
II - Optic	Optic nerve/chiasm, occipital lobe	Vision	Visual field defects (e.g., hemianopia, scotomas), loss of visual acuity.
III - Oculomotor	Midbrain	Eye movement (superior, medial, inferior recti; inferior oblique), pupil constriction, eyelid elevation	Ptosis, diplopia, dilated pupil, eye deviates "down and out".
IV - Trochlear	Midbrain	Eye movement (superior oblique muscle)	Vertical diplopia, eye drifts upward, difficulty reading or going downstairs.
V - Trigeminal	Pons	Facial sensation (ophthalmic, maxillary, mandibular branches), mastication	Loss of facial sensation, jaw deviation toward the side of the lesion.
VI - Abducens	Pons	Eye movement (lateral rectus muscle)	Inability to abduct the eye, horizontal diplopia.
VII - Facial	Pons	Facial expression, taste (anterior 2/3 of tongue), salivation, lacrimation	Facial asymmetry, loss of taste, decreased salivation and lacrimation (Bell's palsy).
VIII - Vestibulocochlear	Pons/medulla junction	Hearing and balance	Hearing loss, vertigo, nystagmus, balance issues.
IX - Glossopharyngeal	Medulla	Taste (posterior 1/3 of tongue), swallowing, salivation (parotid gland)	Loss of taste, impaired gag reflex, difficulty swallowing.
X - Vagus	Medulla	Parasympathetic innervation (heart, lungs, digestive tract), speech, swallowing	Dysphagia, hoarseness, uvula deviates away from lesion side.

Cranial Nerve (CN)	Location	Function	Features of Injury
XI - Accessory	Medulla/spinal cord	Shoulder shrug, head turning (sternocleidomastoid and trapezius muscles)	Weakness in shoulder elevation, impaired head rotation.
XII - Hypoglossal	Medulla	Tongue movement	Tongue deviation toward the lesion side, atrophy, and fasciculations.

Key Points for Clinical Assessment

- **CN I**: Test with smell (e.g., coffee or vanilla).
- **CN II**: Visual acuity and field testing.
- **CN III, IV, VI**: Assess eye movements, pupil reaction, and ptosis.
- **CN V**: Test facial sensation and jaw strength.
- **CN VII**: Check facial symmetry, taste, and eye closure strength.
- **CN VIII**: Hearing tests and balance assessment.
- **CN IX and X**: Test gag reflex, palate elevation, and speech.
- **CN XI**: Assess shoulder shrug and head-turning strength.
- **CN XII**: Evaluate tongue protrusion and strength.

Cranial nerve locations

- **4 CN are above pons (I,II,III,IV).**
- **4 CN exit the pons (V,VI,VII,VIII).**
- **4 CN are in medulla (IX,X,XI,XII).**

Cranial nerve reflexes

Reflex	Afferent limb	Efferent limb
Corneal	Ophthalmic nerve (V_1)	Facial nerve (VII)
Jaw jerk	Mandibular nerve (V_3)	Mandibular nerve (V_3)
Gag	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Carotid sinus	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Pupillary light	Optic nerve (II)	Oculomotor nerve (III)
Lacrimation	Ophthalmic nerve (V_1)	Facial nerve (VII)

Brain stem (Mid brain, Pons, Medulla Oblongata) lesions are typically characterized by ipsilateral cranial nerve involvement and contralateral body involvement.

Lesions of the **cerebellopontine angle** causes compression of cranial nerves **V** (trigeminal), **VII** (facial) and **VIII** (vestibulocochlear).

Lesions at the jugular foramen

- **Nasopharyngeal carcinoma is the commonest cause.**
- **Affected CN → 9,10,11**
  - ⇨ CN IX (Glossopharyngeal nerve) & CN X (Vagus nerve) → palatal weakness and swallowing difficulties , **Laryngeal muscle paralysis would result in bovine cough and husky voice.**
  - ⇨ CN XI (Accessory nerve) → shoulder and sternocleidomastoid weakness

Optic nerve palsy

Aspect	Description
Nerve Anatomy	- Originates in the retina - Continues as the optic nerve - Crosses at the optic chiasm - Extends to the lateral geniculate nucleus (LGN) and visual cortex
Function	- Transmits visual information from the retina to the brain for visual processing
Causes	- Ischaemic optic neuropathy (e.g., hypertension, diabetes) - Optic neuritis (associated with multiple sclerosis) - Compressive lesions (e.g., tumours, aneurysms) - Trauma - Toxic or nutritional deficiencies (e.g., methanol poisoning, vitamin B12 deficiency)
Features of Injury	- Visual loss (decreased visual acuity, usually unilateral) - Visual field defects (central scotoma, complete vision loss, altitudinal field loss) - Afferent pupillary defect (Marcus Gunn Pupil) - Pain, especially with eye movement (seen in optic neuritis) - Colour vision impairment (e.g., red desaturation)
Clinical Examination	- **Visual Acuity Test**: Reduced acuity in the affected eye - **Pupillary Light Reflex**: Presence of a relative afferent pupillary defect (RAPD) on the swinging flashlight test - **Visual Field Testing**: Detects field defects such as central scotoma or hemianopia - **Fundoscopy**: May show optic disc swelling (papillitis) or pallor in chronic cases - **Colour Vision Test**: Red desaturation or reduced colour discrimination in the affected eye

Oculomotor (third nerve) palsy

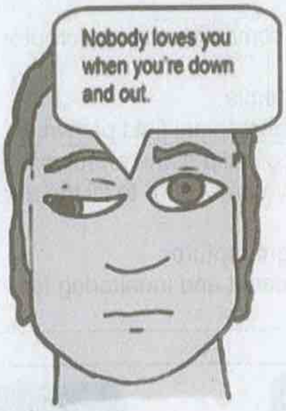
Aspect	Description
Nerve Anatomy	- Originates in the midbrain - Exits the brainstem at the level of the interpeduncular fossa - Innervates the superior, medial, and inferior rectus muscles, inferior oblique, levator palpebrae superioris - Carries parasympathetic fibres for pupil constriction
Function	- Controls most eye movements (upward, downward, and inward) - Elevates the eyelid - Constricts the pupil (via parasympathetic fibres)
Causes	- Ischaemic neuropathy (e.g., diabetes, hypertension) - Aneurysms (e.g., posterior communicating artery) - Tumours - Trauma - Increased intracranial pressure - Demyelinating diseases (e.g., multiple sclerosis)
Features of Injury	- **Ptosis**: Drooping of the upper eyelid - **Ophthalmoplegia**: Impaired eye movements, with the eye deviating "**down and out**" (due to unopposed action of the lateral rectus and superior oblique muscles) - **Dilated pupil**: Non-reactive to light if parasympathetic fibres are involved - **Diplopia**: Double vision due to misalignment of the eyes
Clinical Examination	- **Pupil Assessment**: Check for anisocoria and pupil reactivity; a dilated pupil suggests parasympathetic involvement - **Eye Movement Testing**: Assess the ability to move the eye up, down, and medially - **Ptosis Evaluation**: Note the extent of eyelid drooping - **Swinging Flashlight Test**: May show relative afferent pupillary defect if optic nerve involvement is present - **Fundoscopy**: Usually normal but may show optic nerve issues if associated with compressive lesions

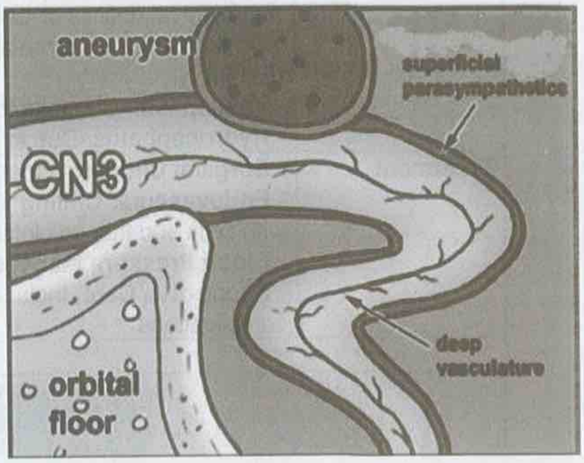
Ipsilateral 3rd CN palsy + contralateral hemiplegia → Weber's syndrome
Ipsilateral 3rd CN palsy + contralateral hemiataxia → Benedikt syndrome
Ipsilateral 3rd CN palsy + ipsilateral hemiparesis + Contralateral homonymous hemianopsia → Uncal herniation

Raised ICP can cause a third nerve palsy due to herniation

Painful third nerve palsy = posterior communicating artery aneurysm

Compression of the oculomotor nerve can cause **isolated pupillary dilation** due to injury of the parasympathetic fibers.
Microangiopathy (e.g., due to diabetes mellitus) typically affects the deeper somatic fibers first, causing **ophthalmoplegia without pupillary dilation**

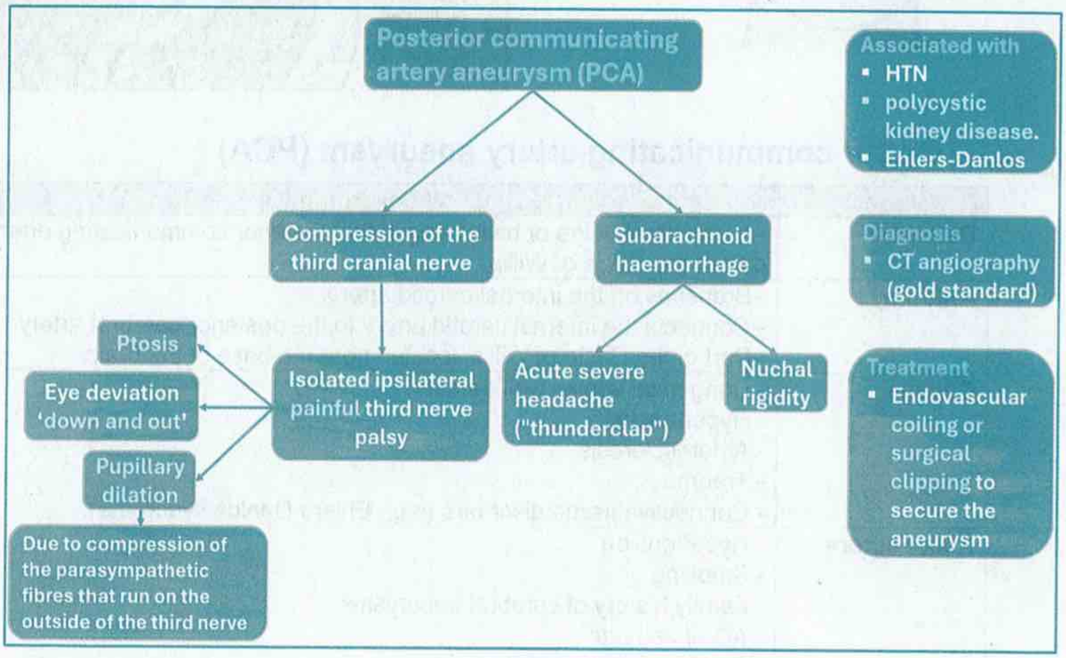




Posterior communicating artery aneurysm (PCA)

Aspect	Description
Definition	An abnormal bulge or ballooning in the posterior communicating artery, part of the Circle of Willis.
Anatomy	- Branches off the internal carotid artery - Connects the internal carotid artery to the posterior cerebral artery - Part of the Circle of Willis, located near the base of the brain
Causes	- Congenital vessel wall defects - Hypertension - Atherosclerosis - Trauma - Connective tissue disorders (e.g., Ehlers-Danlos syndrome)
Risk Factors	- Hypertension - Smoking - Family history of cerebral aneurysms - Advanced age - Certain genetic conditions
Clinical Features	- **Third Nerve Palsy**: Ptosis, eye deviating "down and out," pupil dilation (due to compression of the oculomotor nerve) - **Headache**: Sudden and severe ("thunderclap headache") if rupture occurs - **Visual Disturbances**: Blurred vision or double vision - **Pain**: Periorbital or retro-orbital pain - **Possible Subarachnoid Hemorrhage**: Signs include neck stiffness, photophobia, altered consciousness

Aspect	Description
Diagnosis	- **CT Scan**: Initial imaging for suspected subarachnoid hemorrhage - **CT Angiography (CTA)** or **Magnetic Resonance Angiography (MRA)**: To visualise the aneurysm - **Cerebral Angiography**: Gold standard for detailed aneurysm imaging
Complications	- **Rupture**: Leading to subarachnoid hemorrhage and potentially severe neurological deficits or death - **Compression of Cranial Nerves**: Most commonly the oculomotor nerve (CN III) - **Vasospasm**: Can lead to secondary ischemia - **Hydrocephalus**: Due to blockage of cerebrospinal fluid pathways
Treatment	- **Surgical Clipping**: Open surgery to place a clip at the aneurysm neck - **Endovascular Coiling**: Minimally invasive procedure to fill the aneurysm with coils and induce clotting - **Blood Pressure Management**: To prevent rupture - **Supportive Care**: Includes pain management and monitoring for complications



Trigeminal neuralgia

Aspect	Description
Definition	A chronic pain condition characterised by sudden, severe, and recurrent episodes of facial pain along the distribution of the trigeminal nerve (CN V).
Anatomy	- Involves the trigeminal nerve, which has three branches: ophthalmic (V1), maxillary (V2), and mandibular (V3) - Pain most commonly affects the maxillary (V2) and mandibular (V3) branches
Causes	- **Primary (Idiopathic)**: No identifiable structural cause - **Secondary**: Compression by a blood vessel (e.g., superior cerebellar artery), multiple sclerosis, tumour, or arteriovenous malformation
Risk Factors	- Age over 50 years - Female gender - Family history of trigeminal neuralgia - Multiple sclerosis
Clinical Features	- **Sudden, severe, lancinating facial pain** that may be triggered by activities such as chewing, talking, or touching the face - **Unilateral pain** typically lasting from a few seconds to minutes - Pain episodes may occur in clusters over weeks or months, followed by remission periods - **Trigger zones**: Areas on the face where light touch can provoke pain
Diagnosis	- **Clinical Diagnosis** based on history and characteristic pain features - **MRI**: To rule out secondary causes such as tumours or multiple sclerosis lesions
Complications	- **Chronic Pain**: Can lead to significant impairment in quality of life - **Depression and Anxiety**: Due to chronic nature and severity of pain - **Weight Loss**: From avoiding eating due to pain triggers
Treatment	- **First-Line**: **Carbamazepine** (anticonvulsant; dose typically starting at 100-200 mg/day, gradually titrated up) - **Alternative Medications**: Oxcarbazepine, gabapentin, or baclofen - **Surgical Options**: Microvascular decompression, percutaneous rhizotomy, or gamma knife radiosurgery for refractory cases - **Supportive Care**: Pain management and patient education on avoiding triggers

Trigeminal neuralgia - carbamazepine is first-line

Abducens (VIth) nerve palsy

Aspect	Description
Nerve Anatomy	- Originates in the pons - Exits the brainstem at the pontomedullary junction - Innervates the lateral rectus muscle, responsible for abducting the eye
Function	- Controls lateral movement of the eye (abduction)
Causes	- **Ischaemic neuropathy** (e.g., diabetes, hypertension) - **Increased intracranial pressure** (e.g., tumour, hydrocephalus) - **Trauma** - **Infections** (e.g., meningitis) - **Demyelinating diseases** (e.g., multiple sclerosis) - **Compression** (e.g., aneurysms, tumours)
Features of Injury	- **Horizontal diplopia**: Double vision, worse when looking toward the side of the affected eye - **Inability to abduct the eye**: The affected eye cannot move laterally past the midline - **Esotropia**: The eye may appear to be turned inward when looking straight ahead
Clinical Examination	- **Ocular Motility Test**: Assess eye movement by asking the patient to follow an object laterally; the affected eye will not move fully outward - **Cover-Uncover Test**: May reveal misalignment (esotropia) - **Visual Acuity and Fields**: Typically normal, as the defect is in movement rather than vision - **Neurological Exam**: Evaluate for signs of increased intracranial pressure or other cranial nerve involvement
Findings	- **Restricted lateral gaze** on the affected side - **Esotropia at rest** - **Diplopia** that resolves when looking straight or away from the affected side
Diagnosis	- **Clinical Evaluation** based on eye movement tests - **MRI or CT Scan**: To rule out compressive lesions, increased intracranial pressure, or brainstem pathology - **Blood Tests**: May be indicated for systemic causes like diabetes or infections
Treatment	- **Treat Underlying Cause**: Address conditions such as diabetes, increased intracranial pressure, or infections - **Prism Glasses**: May help manage diplopia - **Botulinum Toxin Injections**: Can be used to temporarily paralyse the medial rectus muscle - **Surgical Correction**: Considered for chronic or unresolved cases

	Abducens nerve palsy • **The patient is unable to abduct the right eye.** • **Abducens nerve innervates the ipsilateral lateral rectus muscle that is necessary for lateral movement of the eye.**

In patients with diplopia the 'cover test' can be used to determine the eye that has the problem.

- **On covering the affected eye, the outermost image disappears.**
- **eg : diplopia on right horizontal gaze , improved on covering the right eye → the right abducens is affected**

Which nerve passes alongside the internal carotid artery within the cavernous sinus?

- **Cranial nerve VI, the abducens nerve.**

Facial (VII) nerve

Aspect	Description
Nerve Anatomy	- Originates in the pons - Travels through the internal auditory canal and exits the skull via the stylomastoid foramen - Divides into five major branches: temporal, zygomatic, buccal, mandibular, and cervical
Function	- Controls muscles of facial expression - Provides taste sensation to the anterior 2/3 of the tongue - Innervates the stapedius muscle in the ear - Controls lacrimation and salivation (submandibular and sublingual glands)
Causes of Injury	- **Bell's Palsy** (idiopathic, most common) - **Infections** (e.g., herpes simplex virus, Ramsay Hunt syndrome) - **Trauma** (e.g., skull fracture) - **Tumours** (e.g., parotid gland tumours) - **Stroke** (affecting upper motor neurons) - **Demyelinating diseases** (e.g., multiple sclerosis)
Features of Injury	- **Peripheral Lesion**: Complete ipsilateral facial weakness (inability to raise eyebrows, close eyes, or smile) - **Central Lesion**: Contralateral lower facial weakness with sparing of the forehead due to bilateral cortical innervation - **Loss of Taste**: Anterior 2/3 of the tongue - **Hyperacusis**: Increased sensitivity to sound (stapedius muscle dysfunction) - **Dry Eye or Reduced Lacrimation**: Affected lacrimal gland function

Aspect	Description
Clinical Examination	- **Facial Movement**: Ask the patient to raise their eyebrows, close their eyes tightly, smile, and puff out their cheeks; assess for asymmetry and weakness - **Taste Test**: Assess taste on the anterior 2/3 of the tongue - **Hearing Test**: Evaluate for hyperacusis - **Schirmer's Test**: To assess lacrimation if dry eye symptoms are present
Findings	- **Complete Facial Paralysis**: Indicates peripheral nerve involvement (e.g., Bell's palsy) - **Forehead Sparing**: Suggests an upper motor neuron lesion (e.g., stroke) - **Loss of Taste** and **Hyperacusis** in more severe cases - **Involvement of Other Cranial Nerves**: Suggests broader pathology (e.g., brainstem lesion)
Diagnosis	- **Clinical Diagnosis** based on examination and history - **MRI or CT Scan**: If a central lesion or tumour is suspected - **Electroneurography (ENoG)** or **Electromyography (EMG)**: To assess nerve function in severe cases - **Blood Tests**: For systemic causes such as Lyme disease or viral infections
Treatment	- **Steroids**: Prednisone for Bell's palsy (e.g., 60-80 mg daily for 5 days, taper over 5 days) - **Antiviral Therapy**: Considered for Bell's palsy with suspected viral etiology (e.g., acyclovir) - **Eye Protection**: Artificial tears and eye patches to prevent corneal damage in cases with incomplete eyelid closure - **Physical Therapy**: To maintain muscle tone and prevent contractures - **Surgical Options**: For cases involving tumour or severe trauma

Comparison of Bell's Palsy and Ramsay Hunt Syndrome

Aspect	Bell's Palsy	Ramsay Hunt Syndrome
Definition	Idiopathic, acute peripheral facial nerve (VII) palsy.	Peripheral facial nerve (VII) palsy caused by reactivation of the varicella-zoster virus (VZV) in the geniculate ganglion.
Cause	Largely idiopathic, though often associated with viral infections (e.g., herpes simplex virus).	Reactivation of VZV, the same virus that causes chickenpox and shingles.
Symptoms	- Sudden onset of unilateral facial paralysis - Inability to raise the eyebrow, close the eye, or smile on the affected side - May have mild pain or discomfort around the jaw or behind the ear.	- Unilateral facial paralysis similar to Bell's palsy - **Vesicular rash in the ear canal, auricle, or oral mucosa** - Severe ear pain (otalgia) - Possible hearing loss and vertigo due to involvement of the vestibulocochlear nerve (CN VIII).
Associated Findings	- Reduced taste sensation on the anterior 2/3 of the tongue - Hyperacusis (increased sound sensitivity).	- Rash in or around the ear - Hearing loss, tinnitus, and vertigo - Loss of taste on the anterior 2/3 of the tongue if affected.

Aspect	Bell's Palsy	Ramsay Hunt Syndrome
Diagnosis	- Clinical diagnosis based on presentation - MRI or CT if atypical features or prolonged symptoms.	- Clinical diagnosis with confirmation of vesicular rash - MRI or CT if needed for atypical or prolonged cases.
Prognosis	- Generally good, with most patients recovering within weeks to months - Some may have residual weakness or synkinesis.	- Less favourable than Bell's palsy - Longer recovery time and higher risk of permanent facial weakness or hearing loss.
Treatment	- **Steroids**: Prednisone (60-80 mg daily for 5 days, taper over 5 days) - **Antivirals**: **Often not necessary** but may be used if viral etiology is suspected (e.g., acyclovir).	- **Steroids**: Prednisone similar to Bell's palsy - **Antivirals**: Acyclovir or valacyclovir to combat VZV - **Pain management**: Analgesics for severe ear pain.
Complications	- Rarely results in permanent facial weakness - Synkinesis (involuntary muscle movements).	- Higher risk of permanent facial weakness - Hearing loss, tinnitus, and persistent vertigo.

vesicular rash around the ear (or anterior 2/3rds of the tongue and the soft palate): suggest a diagnosis of Ramsey Hunt syndrome.

Key Points

- **Bell's Palsy** is idiopathic and often associated with mild viral triggers, presenting with facial paralysis and usually a good recovery.
- **Ramsay Hunt Syndrome** is due to VZV reactivation, characterized by facial paralysis, ear pain, and a vesicular rash, with a more severe prognosis and potential for complications such as hearing loss.

Branches of the Facial Nerve

Facial Palsy + convergent squint
↓
lesion in Pons
as VI th is encircled by VII th

Facial nerve paralysis is often accompanied by:
- **loss of taste**
- **hyperacusis**
- **decreased salivation.**

Acoustic Neuroma (Vestibular Schwannoma)

Aspect	Description
Definition	A benign, slow-growing tumour that develops from the Schwann cells covering the vestibulocochlear nerve (CN VIII).
Anatomy	- Originates in the internal auditory canal - Often extends into the cerebellopontine angle - Can compress adjacent structures such as the cerebellum, brainstem, and other cranial nerves (e.g., CN V, CN VII)
Causes	- Usually sporadic - Associated with **neurofibromatosis type 2 (NF2)** when bilateral - Genetic mutation affecting the NF2 gene on chromosome 22
Clinical Features	- **Hearing Loss**: Progressive, unilateral sensorineural hearing loss is **the most common initial** symptom - **Tinnitus**: Persistent ringing in the affected ear - **Balance Issues**: Vertigo or unsteadiness due to vestibular involvement - **Facial Numbness or Weakness**: Due to compression of the trigeminal or facial nerve - **Headaches**: May occur in larger tumours that increase intracranial pressure
Diagnosis	- **Audiometry**: To assess hearing loss - **MRI with Contrast**: Gold standard for visualising the tumour and its extent - **CT Scan**: Used if MRI is contraindicated
Complications	- **Hearing Loss**: Permanent hearing damage if untreated - **Facial Nerve Paralysis**: Due to tumour compression or surgical intervention - **Hydrocephalus**: Large tumours can block cerebrospinal fluid pathways, leading to increased intracranial pressure - **Cerebellar Dysfunction**: Large tumours may affect coordination and balance
Treatment	- **Observation**: For small, asymptomatic tumours, especially in older patients - **Stereotactic Radiosurgery (e.g., Gamma Knife)**: Non-invasive treatment to stop tumour growth - **Microsurgical Removal**: Indicated for large or symptomatic tumours; risks include hearing loss and facial nerve damage - **Hearing Rehabilitation**: Cochlear implants or hearing aids if hearing is compromised

Loss of corneal reflex → think acoustic neuroma

Labyrinthine Infarction vs Viral Labyrinthine Dysfunction

Feature	Labyrinthine Infarction	Viral Labyrinthine Dysfunction
Definition	Ischaemia or infarction of the labyrinthine artery, leading to acute vestibular and auditory symptoms.	Viral infection or inflammation of the inner ear structures (labyrinth), causing acute vestibular dysfunction.
Aetiology	- Thromboembolism (e.g., small vessel disease). - Vertebrobasilar ischaemia.	- Viral infections (e.g., herpes simplex virus, influenza). - Post-viral immune-mediated inflammation.
Onset	Sudden, severe onset.	Subacute or gradual onset over hours to days.
Symptoms	- Sudden severe vertigo. - Sudden hearing loss (sensorineural). - Nausea and vomiting. - Tinnitus.	- Vertigo (lasting hours to days). - Mild hearing changes (not always present). - Nausea and vomiting.
Duration	Persistent symptoms with little fluctuation, unless treated.	Resolves over days to weeks, often self-limiting.
Associated Neurological Signs	May have signs of vertebrobasilar insufficiency (e.g., diplopia, dysarthria, ataxia).	No associated neurological signs; isolated to the inner ear.
Audiovestibular Testing	- Audiometry: Sensorineural hearing loss. - Vestibular testing: Absent caloric response in the affected ear.	- Audiometry: Mild or no hearing loss. - Vestibular testing: Reduced or absent caloric response.
Imaging Findings	- MRI with diffusion-weighted imaging (DWI): Evidence of infarction in the inner ear or brainstem (vertebrobasilar area).	- MRI: May show enhancement of the labyrinth on contrast studies (indicating inflammation).
Treatment	- Urgent management: Antiplatelets or anticoagulation (if embolic). - Address vascular risk factors.	- Symptomatic treatment: Vestibular suppressants (e.g., meclizine, prochlorperazine). - Corticosteroids in severe cases.
Prognosis	- Poor prognosis for hearing recovery; persistent auditory and vestibular deficits are common.	- Good prognosis; most recover completely, though some may have mild residual vestibular dysfunction.

Key Differences:

1. **Onset**:
   - Labyrinthine infarction: Abrupt and severe.
   - Viral dysfunction: Gradual or subacute.
2. **Neurological signs**:
   - Present in infarction if associated with vertebrobasilar insufficiency.
   - Absent in viral dysfunction.
3. **Imaging**:
   - Infarction: Confirmed by MRI (DWI).
   - Viral dysfunction: May show inflammation on contrast MRI.

Key Points for MRCP:

- Labyrinthine infarction should be **urgently investigated** as it may indicate vertebrobasilar ischaemia.
- Viral labyrinthitis is **self-limiting** in most cases, but corticosteroids may aid recovery in severe cases.

Sudden-onset unilateral hearing loss → consider Labyrinthine infarction typically due to anterior cerebellar artery dissection after minor head trauma

Ptosis, Miosis and Mydriasis

Feature	Description	Causes	Associated Conditions
Ptosis	Drooping of the upper eyelid, which may be partial or complete.	- **Horner's Syndrome**: Due to sympathetic pathway disruption - **Third Nerve Palsy**: Oculomotor nerve dysfunction - **Myasthenia Gravis**: Autoimmune disorder affecting neuromuscular junction - **Trauma or Tumours**: Affecting the oculomotor nerve or levator palpebrae superioris muscle	- **Horner's Syndrome**: Ptosis with miosis and anhidrosis - **Third Nerve Palsy**: Ptosis with "down and out" eye position and pupil dilation - **Myasthenia Gravis**: Fluctuating ptosis that worsens with fatigue
Miosis	Constriction of the pupil, which results in a smaller-than-normal pupil size.	- **Horner's Syndrome**: Sympathetic pathway disruption - **Opioid Use**: Pupillary constriction due to drug effects - **Pontine Lesions**: Affecting brainstem pathways	- **Horner's Syndrome**: Miosis with ptosis and anhidrosis - **Opioid Intoxication**: Bilaterally constricted pupils - **Pontine Stroke**: Bilateral pinpoint pupils
Mydriasis	Dilation of the pupil, resulting in a larger-than-normal pupil size.	- **Third Nerve Palsy**: Oculomotor nerve dysfunction affecting parasympathetic fibres - **Brainstem Lesions**: Affecting parasympathetic pathways - **Drug Use**: Stimulants such as cocaine or anticholinergic agents (e.g., atropine)	- **Third Nerve Palsy**: Mydriasis with ptosis and "down and out" eye position - **Anticholinergic Toxicity**: Dilated pupils with dry skin and hyperthermia - **Brainstem Injury**: Can present with fixed and dilated pupils

Key Points

- **Ptosis** may indicate conditions involving the sympathetic or parasympathetic pathways (e.g., Horner's syndrome, third nerve palsy) or neuromuscular issues (e.g., myasthenia gravis).
- **Miosis** is commonly seen in Horner's syndrome or due to drug effects like opioids, while bilateral miosis may suggest brainstem involvement.
- **Mydriasis** suggests dysfunction in the oculomotor nerve, brainstem lesions, or exposure to certain drugs (e.g., anticholinergics).

Ptosis + dilated pupil → Third nerve palsy

Ptosis + constricted pupil → Horner's

Orbital apex syndrome caused by pathology affects the cranial nerves passing through the orbital apex (CN II, III, IV, V1, VI), leading to vision loss, ophthalmoplegia, ptosis, and reduced sensation in the ophthalmic division of the trigeminal nerve.

Horner's syndrome

Aspect	Description
Definition	A neurological condition resulting from disruption of the sympathetic pathway that supplies the eye and face, leading to a characteristic triad of symptoms.
Anatomy	- The sympathetic pathway is a three-neuron pathway: - **First-order neuron**: Originates in the hypothalamus and descends to the cervical spinal cord (C8-T2). - **Second-order neuron**: Travels from the spinal cord to the superior cervical ganglion. - **Third-order neuron**: Extends from the superior cervical ganglion to the eye and facial sweat glands.
Causes	- **Central Lesions**: Brainstem stroke, multiple sclerosis, tumour compressing the sympathetic tract. - **Preganglionic Lesions**: Trauma, tumour (e.g., Pancoast tumour), cervical spinal cord lesions. - **Postganglionic Lesions**: Carotid artery dissection, cluster headaches, trauma.
Clinical Features	- **Ptosis**: Mild drooping of the upper eyelid due to weakness of the Muller's muscle. - **Miosis**: Constricted pupil due to unopposed parasympathetic action. - **Anhidrosis**: Decreased sweating on the affected side of the face (varies depending on the lesion location). - **Enophthalmos**: The appearance of a sunken eye (subjective). - **Delayed Pupil Dilation**: Sluggish response of the affected pupil to dim light.

Aspect	Description
Diagnosis	- **Clinical Examination**: Assess for ptosis, miosis, and anhidrosis. - **Cocaine Test**: Cocaine drops do not dilate the affected pupil. - **Apraclonidine Test**: Causes dilation of the affected pupil due to supersensitivity of the alpha receptors. - **Imaging**: MRI or CT to identify underlying lesions (e.g., Pancoast tumour, carotid dissection).
Associated Conditions	- **Pancoast Tumour**: Apical lung tumour affecting the sympathetic chain. - **Carotid Artery Dissection**: Can cause acute onset Horner's syndrome with headache or neck pain. - **Cluster Headaches**: May present with temporary Horner's syndrome during headache episodes.
Treatment	- **Treat Underlying Cause**: Surgical resection for tumours, anticoagulation for carotid artery dissection, or management of associated conditions. - **Supportive Care**: No specific treatment for Horner's syndrome itself; management focuses on the underlying condition.

Key Points

- **Classic Triad**: Ptosis, miosis, and anhidrosis.
- **Central vs. Peripheral Lesions**: Central lesions may involve the brainstem or spinal cord, while peripheral lesions often involve the neck or face.
- **Diagnostic Tests**: Apraclonidine and cocaine tests can confirm Horner's syndrome, while imaging helps identify the cause.

Horner's syndrome : triad of ptosis, miosis and anhydrosis

Horner's syndrome: anhydrosis determines site of lesion:

- **Head, arm, trunk → central lesion : stroke, syringomyelia**
- **Just face → pre-ganglionic lesion : Pancoast, cervical rib**
- **Absent → post-ganglionic lesion : carotid artery**

Distinguishing between causes

- **Heterochromia (difference in iris colour) is seen in congenital Horner's**
- Anhydrosis: see the table below

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the face	No anhydrosis
➲ Stroke ➲ Syringomyelia ➲ Multiple sclerosis ➲ Tumour ➲ Encephalitis	➲ Pancoast's tumour ➲ Thyroidectomy ➲ Trauma ➲ Cervical rib	➲ Carotid artery dissection ➲ Carotid aneurysm ➲ Cavernous sinus thrombosis ➲ Cluster headache

Because the sympathetic plexus accompanying the internal carotid artery innervates sweat glands only to the medial forehead, facial anhydrosis is only partial when Horner's syndrome is caused by postganglionic lesions.

Bulbar and Pseudobulbar palsy

Comparison of Bulbar and Pseudobulbar Palsy

Feature	Bulbar Palsy	Pseudobulbar Palsy
Definition	Lower motor neuron (LMN) lesion affecting cranial nerves IX, X, XI, and XII.	**Upper motor neuron (UMN) lesion** affecting corticobulbar tracts supplying cranial nerves IX, X, XI, and XII.
Aetiology	- Brainstem lesions (e.g., motor neuron disease). - Peripheral nerve diseases (e.g., Guillain-Barré syndrome). - Neuromuscular junction diseases (e.g., myasthenia gravis).	- Bilateral UMN lesions (e.g., cerebrovascular disease, multiple sclerosis). - Neurodegenerative diseases (e.g., progressive supranuclear palsy). - Traumatic brain injury, severe infections.
Speech	Nasal, slurred, or hoarse speech (dysarthria).	Spastic, strained, and slow speech.
Swallowing	Dysphagia, especially for liquids, with nasal regurgitation.	Dysphagia with difficulty initiating swallowing and coughing during meals.
Emotional lability	Absent.	Present (inappropriate laughing or crying).
Tongue	Weakness, atrophy, and fasciculations.	No atrophy or fasciculations; may be spastic and stiff.
Jaw jerk reflex	Absent or normal.	Exaggerated or brisk.
Gag reflex	Reduced or absent.	Normal or hyperactive.
Neurological findings	LMN signs: muscle atrophy, fasciculations.	**UMN signs:** spasticity, brisk reflexes.

Key Differences

- **Bulbar Palsy** involves lower motor neuron lesions with features like tongue atrophy and fasciculations.
- **Pseudobulbar Palsy** involves upper motor neuron lesions with exaggerated reflexes and emotional lability.
- **Gag Reflex and Jaw Jerk**: Reduced or absent in bulbar palsy; hyperactive in pseudobulbar palsy.
- **Emotional Lability**: Characteristic of pseudobulbar palsy due to UMN involvement.

Movement, seizures and cognitive disorders

Epilepsy

Definitions

- **Epilepsy**: A chronic neurological disorder defined by either two or more unprovoked or reflex seizures separated by more than 24 hours or one seizure with a high risk of recurrence (e.g., post-traumatic brain injury, stroke).
- **Reflex Epilepsy**: Seizures consistently triggered by specific stimuli (e.g., photosensitivity, music, hormonal changes like catamenial epilepsy).
- **Drug-Resistant Epilepsy**: Epilepsy where at least two AEDs have failed to control seizures.
- **Resolved Epilepsy:** No seizures for 10 years and off AEDs for the last 5 years.
- **Status Epilepticus**: Continuous seizure lasting ≥5 minutes or recurrent seizures without recovery in between.

Types of Seizures

- **Generalised Seizures**:
    - **Tonic-Clonic (Grand Mal)**: Loss of consciousness with muscle stiffening followed by jerking.
    - **Absence Seizures**: Brief, blank stare without postictal confusion; common in children.
- **Partial Seizures**:
    - **Simple Partial**: No impairment of consciousness.
    - **Complex Partial**: Impaired awareness, often with automatisms.
    - **Jacksonian Seizure**: Spreads from one muscle group to others; preserved consciousness.
    - **Temporal Lobe Epilepsy**: Automatisms (e.g., repetitive chewing); associated with hippocampal sclerosis.
    - **Gelastic Seizures**: Involuntary laughter or crying, often due to hypothalamic hamartomas.
- **Atonic Seizures**: Sudden loss of muscle tone, mistaken for syncope.
- **Somatosensory Seizures**: Tingling spreading in seconds; linked to parietal lobe.

Investigations

- **EEG**: Supports diagnosis; **normal EEG does not exclude epilepsy.**
- **Neuroimaging**: to identify underlying gross pathology. MRI preferred; CT as an alternative if MRI unavailable or contraindicated.

Treatment

- **When to Start AEDs**:
    - After a second seizure or a first seizure with risk factors (neurological deficits, structural abnormalities on imaging, epileptic activity on EEG).
    - Start with monotherapy, gradually titrating the dose.

Drug of Choice by Seizure Type:

Seizure Type	First-Line Treatment	Second-Line Treatment
Focal Seizures	Lamotrigine, Carbamazepine	Levetiracetam, Valproate
Generalised Tonic-Clonic	Valproate, Lamotrigine	Levetiracetam
Absence Seizures	Ethosuximide	Valproate, Lamotrigine
Myoclonic Seizures	Valproate	Levetiracetam
Atonic Seizures	Valproate	Lamotrigine

Antiepileptic Drugs (AEDs) Summary

Drug	Mechanism	Dose	Side Effects
Benzodiazepines	↑ GABA action	Varies (e.g., lorazepam 2 mg IV)	Sedation, dependence, respiratory depression
Phenytoin	Inhibits sodium channels	100 mg TID	Gum hypertrophy, teratogenicity, ataxia
Carbamazepine	Sodium channel blocker	100-200 mg BID	Diplopia, ataxia, SIADH, rash (SJS)
Ethosuximide	Blocks T-type Ca2+ channels	250 mg/day	GI upset, SJS
Lamotrigine	Sodium channel blocker, ↓ glutamate	25 mg/day, titrate slowly	Rash, SJS, hemophagocytic syndrome
Valproate	↑ GABA, Na+ channel inactivation	250-500 mg/day	Hepatotoxicity, weight gain, teratogenicity
Levetiracetam	Unknown, affects SV2A	500 mg BID	Mood changes, fatigue, headache
Topiramate	Blocks Na+ channels, ↑ GABA	25 mg/day	Weight loss, cognitive slowing, kidney stones

Key Points:

- **Valproate** is effective for multiple generalised seizure types but is teratogenic.
- **Lamotrigine** has a favourable side-effect profile but requires slow titration due to the risk of rash.
- **Lamotrigine** is the most appropriate choice for women of child-bearing age because: low risk of congenital malformations. it does not affect the effectiveness of the oral contraceptive pill
- **Carbamazepine** is a common choice for focal seizures but may exacerbate absence and myoclonic seizures.
- **Ethosuximide** is specifically used for absence seizures.
- a patient with epilepsy and hepatic impairment → Topiramate (exclusive renal excretion)
- **Antiepileptic and weight**
    - AEDs induce weight loss: topiramate
    - AEDs induce weight gain: Valproate, vigabatrin, gabapentin, carbamazepine, and pregabalin
    - AEDs weight-neutral: Levetiracetam, lamotrigine, and phenytoin

Special Considerations

- **AEDs in Pregnancy**: Use folic acid 5 mg/day to minimise risks. **Lamotrigine** and **levetiracetam** preferred due to lower teratogenicity.
- **Status Epilepticus Treatment**: **Transfer to an Intensive Therapy Unit**
  - **Initial**: Benzodiazepines (e.g., lorazepam).
  - **Second Line**: IV phenytoin or phenobarbital.
  - **Third Line**: General anaesthesia (e.g., propofol).
- **Stopping AEDs**: Consider after 2+ years seizure-free; taper over 2-3 months.

Pseudoseizures

- **Factors Indicating Pseudoseizures**: Public onset, prolonged (>15 min), pelvic thrusting, tearful episodes, resistance to eye-opening. **Urinary incontinence can also occur in pseudoseizures, but tongue biting is rare.**
- **Diagnosis**: **Video telemetry**.
- **Management: Observation** and addressing underlying psychiatric conditions.

Absence seizure (petit mal)

- **presents with a blank stare, 3 Hz brain waves and do not show postictal confusion.**
- **Good prognosis: 90 -95% become seizure free in adolescence.**

Somatosensory seizures

- **Spread of symptoms ('marching') in seconds**
- **The usual source is the parietal lobe.**
- **Example → tingling sensation starts in fingers and spreads in seconds to affect the whole arm and leg.**

  ☞ **Positive symptoms** (jerking, tingling) usually signify **epilepsy**.
  ☞ **Negative symptoms** (weakness, numbness) are usually caused by transient focal **ischaemia**.

- **Spread of symptoms** ('marching') indicates **migraine (in 5-20 minutes)** or **seizures (in seconds).**

Atonic seizure (also known as "drop seizure" or "drop attack")

- **Sudden loss of muscle tone: sudden head drop or collapse (lasts < 15 seconds)**
- **Frequently mistaken for syncope**

Epilepsy medication: first-line

- generalised seizure: sodium valproate
- partial seizure: carbamazepine

Patients cannot drive for 6 months following a seizure

AED cessation can be considered if seizure free for > 2 years – Stop AEDs over 2-3 months

Juvenile myoclonic epilepsy is the **most common** primary generalised epilepsy, but is underdiagnosed due to lack awareness of the condition by doctors. Typically presenting in adolescence with myoclonic jerks, generalised tonic-clonic seizures, and sometimes absence seizures.

Antiepileptics to Avoid in Myoclonic Seizures or juvenile myoclonic epilepsy → may exacerbate myoclonic seizures.

1. **Carbamazepine**
2. **Oxcarbazepine**
3. **Phenytoin**
4. **Gabapentin**
5. **Pregabalin**
6. **Vigabatrin**
7. **Lamotrigine** (in some cases)

DVLA regulations : for seizure and stroke

Case	Group 1 Car & motorcycle	Group 2 Bus and lorry
First epileptic seizure/isolated seizure	no driving for 6 months.	no driving for 5 years.
Epilepsy or multiple seizures	no driving for 12 months.	must remain seizure-free for 10 years (without epilepsy medication)
Dissociative seizures	no driving for 3 months after event free.	no driving for 3 months after event free.
Withdrawal of epilepsy medication	no driving for 6 months after the last dose.	must remain seizure-free for 10 years (without epilepsy medication).(no special considerations for withdrawal)
Single TIA, Stroke	no driving for 1 month.	no driving for 1 year.
Multiple TIA	no driving for 3 months.	no driving for 1 year.

Tourette Syndrome

Definition: A chronic neurological disorder characterised by the presence of motor and vocal tics.

Epidemiology:

- Onset occurs before 18 years of age.
- More common in males, with a male-to-female ratio of 4:1.
- Many children experience improvement or outgrow the condition over time.

Pathogenesis:

- Caused by a combination of genetic, environmental, and social factors.
- Familial link often observed, associated with abnormalities in the mesolimbic system.

Clinical Features:

- **Motor Tics**: Include movements such as blinking, throat clearing, and shoulder shrugging. Patients often have a premonitory sensation (e.g., an itch) before the tic.
- **Vocal Tics**: Can range from simple sounds to more complex vocalisations, including shouting words or phrases, sometimes involving inappropriate language (coprolalia).
- Tics may occur in episodes and can be exacerbated by stress or excitement.
- Tics often wax and wane over time in terms of frequency and severity.

Associated Conditions:

- Up to 90% of patients have comorbid psychiatric conditions.
- **ADHD (Attention Deficit Hyperactivity Disorder)**: Present in about 60% of cases.
- Other associated conditions include obsessive-compulsive disorder (OCD) and anxiety disorders.

Management:

- **First-Line Treatment**: Cognitive behavioural therapy (CBT), especially habit reversal therapy.
- **Second-Line Treatment**: Pharmacotherapy, including alpha-2 adrenergic agonists such as clonidine and guanfacine.
- More severe cases may require antipsychotic medications or other pharmacological treatments.

Huntington's disease (HD)

Definition:

- A progressive, hereditary neurodegenerative disorder characterised by motor dysfunction, cognitive decline, and psychiatric disturbances.

Genetics:

- Caused by an autosomal dominant mutation in the *HTT* gene on chromosome 4, leading to an expanded CAG trinucleotide repeat.
- The disease shows **anticipation**, with earlier onset in successive generations, especially when inherited from the father.

Pathophysiology:

- Mutant huntingtin protein accumulates and causes neuronal damage, particularly in the **basal ganglia** (striatum) and cerebral cortex.
- Leads to disruption of motor control and cognitive and emotional functions.

Clinical Features:

- **Motor Symptoms:**
  - **Chorea:** Involuntary, rapid, jerky movements.
  - **Dystonia:** Abnormal muscle tone leading to sustained muscle contractions.
  - **Bradykinesia:** Slowness of movement in later stages.
  - **Balance and coordination issues.**
- **Cognitive Decline:**
  - Progressive dementia.
  - Impaired executive functions, such as problem-solving and planning.
- **Psychiatric Symptoms:**
  - Depression, anxiety, irritability.
  - Psychosis or other mood disorders.
  - Personality changes and impulsivity.

Diagnosis:

- **Clinical Assessment:** Based on family history, physical examination, and characteristic symptoms.
- **Genetic Testing:** Confirmatory, identifying the number of CAG repeats in the *HTT* gene.
- **Imaging:** MRI or CT may show atrophy of the caudate nucleus and putamen in advanced stages.

Management:

- **Symptomatic Treatment:**
  - **Motor Symptoms:** Tetrabenazine (dopamine depleting agent), antipsychotics for chorea.
  - **Psychiatric Symptoms:** Antidepressants, mood stabilisers, and antipsychotics as needed.
- **Supportive Care:**
  - Physical therapy for mobility.
  - Speech therapy for communication issues.
  - Occupational therapy for daily living activities.
- **Genetic Counseling:** Essential for affected individuals and at-risk family members.

Prognosis:

- Gradual progression over 10-25 years after onset.
- Typically leads to severe disability and death due to complications like pneumonia or cardiovascular issues.

> **In Huntington disease, increased number of CAG repeats leads to the damage to the Caudate nucleus and results in decreased acetylcholine (Ach) and GABA.**

Parkinsonism

Parkinsonism: Definition and Causes

Aspect	Description
Definition	Parkinsonism refers to a clinical syndrome characterised by bradykinesia (slowness of movement), rigidity, resting tremor, and postural instability. It results from dysfunction of the basal ganglia and dopaminergic pathways.

Causes	Description
Idiopathic Parkinson's Disease	The most common cause; due to degeneration of dopaminergic neurons in the substantia nigra.
Drug-Induced Parkinsonism	Caused by medications that block dopamine receptors, such as antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide).
Vascular Parkinsonism	Results from multiple small strokes affecting the basal ganglia; more common in older adults with vascular risk factors.
Parkinson-Plus Syndromes	Includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration; characterised by additional non-Parkinsonian features.
Toxin-Induced Parkinsonism	Exposure to toxins such as carbon monoxide or manganese.
Trauma-Related	Repeated head trauma, as seen in boxers (e.g., chronic traumatic encephalopathy).
Genetic Disorders	Conditions such as Wilson's disease or Huntington's disease may present with parkinsonism-like features.
Infections	Encephalitis lethargica (historically), HIV-associated neurocognitive disorders.

Parkinson's disease (PD)

Definition:
- Progressive neurodegenerative disorder caused by the degeneration of dopaminergic neurons in the substantia nigra.

Epidemiology:
- Second most common neurodegenerative disorder after Alzheimer's disease.
- Prevalence: 1-2 per 1000 people.
- More common in men (2:1 ratio).
- Mean age of diagnosis: 65 years.

Risk Factors:
- Age > 60 years.
- Male sex.
- Family history.
- Exposure to environmental pesticides.

Pathophysiology:

- **Normal Function**: Dopamine activates the direct (stimulatory) pathway and inhibits the indirect (inhibitory) pathway, facilitating smooth movement.
- **PD Pathology**:
  - Aggregation of α-synuclein proteins → formation of Lewy bodies.
  - Loss of dopamine-producing neurons in the substantia nigra.
  - Reduced dopamine → increased inhibitory output from the globus pallidus → reduced thalamic activity and decreased movement.
- Classic symptoms appear after 50% neuron loss and 75-80% striatal dopamine depletion.

Clinical Features:

- **Motor Symptoms**:
  - **Bradykinesia**: Slow movements, shuffling gait, difficulty initiating movement.
  - **Tremor**: Resting, "pill-rolling" tremor (3-5 Hz), worsens with stress, absent in REM sleep.
  - **Rigidity**: "Lead pipe" or "cogwheel" due to superimposed tremor.
- **Other Features**:
  - Mask-like facies, micrographia, drooling, flexed posture.
  - **Psychiatric**: Depression (common), dementia, psychosis, sleep disturbances.
  - **Early Sign**: REM sleep behaviour disorder (acting out dreams).
  - **Gastrointestinal**: Intestinal pseudo-obstruction in advanced stages.
- **Drug-Induced Parkinsonism**:
  - Rapid onset, usually bilateral.
  - Rigidity and resting tremor are less common.

Diagnosis:

- **Step 1**: Presence of bradykinesia and at least one of the following: muscular rigidity, rest tremor, or postural instability.
- **Step 2**: Exclusion of other conditions (e.g., repeated strokes, head injury, antipsychotic use).
- **Step 3**: Supportive criteria (e.g., unilateral onset, excellent response to levodopa).

Investigations:

- **SPECT Scan**: Used for tremor differentiation when needed.
- **MRI**: To exclude structural abnormalities.

Management:

- **First-Line Treatment**:
  - **Quality of Life Affected**: Levodopa (with carbidopa).
  - **Not Affecting Quality of Life**: Non-ergot dopamine agonist (e.g., ropinirole), levodopa, or MAO-B inhibitor (e.g., selegiline).
  - **> 65 Years**: Levodopa + carbidopa due to motor complications risk.
  - **< 65 Years**: Non-ergot dopamine agonists preferred.
- **Second-Line**: Add MAO-B inhibitors, COMT inhibitors (e.g., entacapone) for motor fluctuations.
- **Third-Line**: Amantadine for dyskinesia.
- **Fourth-Line**: Deep brain stimulation for advanced cases.

Comparison of Anti-Parkinson Drugs:

- **Levodopa**: Best motor symptom improvement but more motor complications.
- **Dopamine Agonists**: Reduce "off" time but intermediate adverse events.
- **MAO-B Inhibitors**: Fewer motor complications.
- **Amantadine**: No significant evidence for motor improvement.

Management of Non-Motor Symptoms:

- **Excessive Daytime Sleepiness**: Modafinil.
- **REM Sleep Disorder**: Clonazepam or melatonin.
- **Nocturnal Akinesia**: Levodopa or oral dopamine agonists.
- **Postural Hypotension**: Midodrine or fludrocortisone if needed.
- **Psychotic Symptoms**: Reduce Parkinson's meds; consider quetiapine or clozapine.
- **Dementia**: Rivastigmine or memantine.
- **Drooling**: Glycopyrronium bromide or botulinum toxin.

Medication Withdrawal:

- Avoid abrupt withdrawal to prevent acute akinesia or parkinsonian malignant syndrome.
- **Parkinsonian Malignant Syndrome**: Similar to neuroleptic malignant syndrome, triggered by sudden medication cessation.

The classic triad of features: bradykinesia, asymmetrical tremor and rigidity

Decreased dopamine impairs movement by which mechanisms?

➲ **Decreased activation of the D1 and D2 receptors**

Which mechanism underlying the neurodegeneration seen in Parkinson's?

➲ **Impaired protein degradation**

➲ Mutations in either the **parkin gene or UCHL1** lead to impaired protein degradation.

➲ **Alpha-synuclein is a synaptic protein accumulates in Lewy body dementia and Parkinson's disease.**

What is the characteristic microscopic finding in Parkinson's disease?

➲ **Lewy body**

The symptoms of Parkinson's disease are characteristically asymmetrical.

Anti-Parkinson drugs

1. Levodopa

- **Mechanism**: Precursor of dopamine; converted to dopamine in the brain to supplement reduced levels.
- **Combined with**: Carbidopa or benserazide to inhibit peripheral breakdown.
- **Benefits**: Most effective for motor symptom improvement.
- **Side Effects**: Nausea, dyskinesia, motor fluctuations, hallucinations.

2. Dopamine Agonists

- **Examples**: Pramipexole, Ropinirole, Apomorphine.
- **Mechanism**: Stimulate dopamine receptors directly.
- **Uses**: First-line in younger patients; adjunct to levodopa in advanced disease.
- **Side Effects**: Nausea, hallucinations, impulse control disorders (e.g., gambling, hypersexuality), drowsiness.

3. MAO-B Inhibitors

- **Examples**: Selegiline, Rasagiline.
- **Mechanism**: Inhibit monoamine oxidase B enzyme, reducing dopamine breakdown.
- **Uses**: Monotherapy in early PD or as an adjunct to levodopa.
- **Side Effects**: Nausea, insomnia, headache.

4. COMT Inhibitors

- **Examples**: Entacapone, Tolcapone.
- **Mechanism**: Inhibit catechol-O-methyltransferase, prolonging the action of levodopa.
- **Uses**: Added to levodopa to reduce "off" periods.
- **Side Effects**: Diarrhoea, liver toxicity (tolcapone), dyskinesia.

5. Amantadine

- **Mechanism**: Increases dopamine release and blocks NMDA receptors.
- **Uses**: Helps with dyskinesia; limited use due to modest effects.
- **Side Effects**: Livedo reticularis, confusion, hallucinations.

6. Anticholinergics

- **Examples**: Trihexyphenidyl, Benztropine.
- **Mechanism**: Reduce cholinergic activity to help balance with reduced dopaminergic activity.
- **Uses**: More effective for tremor control.
- **Side Effects**: Dry mouth, constipation, confusion, urinary retention (caution in elderly).

7. Deep Brain Stimulation (DBS)

- **Mechanism**: Surgical treatment that electrically stimulates specific brain regions (e.g., subthalamic nucleus).
- **Uses**: Advanced PD with inadequate response to medications.
- **Benefits**: Reduces motor symptoms and "off" time.
- **Risks**: Infection, bleeding, mood changes.

Comparison Overview

- **Levodopa**: Best for symptom control but associated with long-term motor complications.
- **Dopamine Agonists**: Lower risk of motor complications but more psychiatric side effects.
- **MAO-B and COMT Inhibitors**: Useful adjuncts to reduce motor fluctuations.
- **Amantadine**: Mainly used for dyskinesia.
- **Anticholinergics**: Effective for tremor; limited by cognitive side effects.

Comparison of Anti-Parkinson Drugs

Aspect	Levodopa	Dopamine Agonists	MAO-B Inhibitors & COMT Inhibitors	Amantadine
Improvement in motor symptoms and activities of daily living	**More improvement**	Less improvement	Less improvement	No evidence of improvement
Off time (Periods when medication effect wears off, worsening Parkinsonian symptoms).	Moderate reduction	More reduction	Moderate reduction	No studies reporting this outcome
Adverse events	**Fewer adverse events**	Intermediate risk	Fewer adverse events	No studies reporting this outcome
Motor complications	**More motor complications**	Fewer motor complications	Fewer motor complications	Not applicable
Hallucinations	**Lower risk**	More risk	Lower risk	No studies reporting this outcome

Of the antiparkinson drugs, levodopa is associated with the greatest improvement in symptoms and activities of daily living

Serotonin syndrome and Neuroleptic malignant syndrome (NMS)

Aspect	Serotonin Syndrome	Neuroleptic Malignant Syndrome (NMS)
Definition	A life-threatening condition due to excessive serotonin activity in the CNS.	A fatal reaction to antipsychotic drugs causing dopamine blockade.
Onset	**Rapid** (within hours of drug intake or dose change).	**Gradual** (days to weeks after starting or increasing dose of antipsychotic).
Causes	- Use of SSRIs, SNRIs, MAOIs, TCAs. - Drug interactions (e.g., SSRI + MAOI). - Recreational drugs (e.g., MDMA, cocaine).	- Antipsychotic drugs (e.g., haloperidol, risperidone). - Dopamine-blocking agents (e.g., metoclopramide).

Aspect	Serotonin Syndrome	Neuroleptic Malignant Syndrome (NMS)
Key Symptoms	- **Mental Status**: Agitation, confusion. - **Neuromuscular**: Hyperreflexia, **clonus**, **myoclonus**. - **Autonomic**: Hyperthermia, tachycardia, diaphoresis, hypertension.	- **Mental Status**: Delirium, stupor, or coma. - **Neuromuscular**: Lead-pipe **rigidity**, bradyreflexia. - **Autonomic**: Hyperthermia, tachycardia, diaphoresis, hypertension.
Distinguishing Features	- **Hyperreflexia and clonus** are characteristic. - Symptoms develop rapidly after drug use.	- **Lead-pipe rigidity** and bradyreflexia. - Gradual onset, often related to neuroleptic drug initiation.
Laboratory Findings	- Elevated creatine kinase (CK) possible. - No specific lab marker; diagnosis is clinical.	- Markedly elevated CK due to muscle breakdown. - Leukocytosis, metabolic acidosis.
Treatment	- Discontinue serotonergic agents. - Supportive care (IV fluids, cooling measures). - Medications: Benzodiazepines for sedation; cyproheptadine (serotonin antagonist).	- Discontinue causative agent. - Supportive care (hydration, cooling). - Medications: Benzodiazepines for sedation; dantrolene or bromocriptine may be used.
Prognosis	Good with prompt recognition and treatment.	Can be severe with significant mortality if not treated promptly.

Key differences

Serotonin syndrome	Neuroleptic malignant syndrome
• develops over 24 hours.	• develops over days to weeks.
• characterized by neuromuscular hyperreactivity (**tremor, hyperreflexia, myoclonus**).	• characterized by sluggish neuromuscular responses (rigidity, bradyreflexia).
• resolution typically requires less than 24 hours	• resolution typically requires an average of nine days.

Anticholinergic syndrome (overdose)

Causes

- **Atropine-containing plants:** Belladonna and Datura poisoning
- **Anticholinergic agents** (e.g., atropine, benztropine, trihexyphenidyl)
- **Drugs with anticholinergic properties:** Tricyclic antidepressants e.g, amitriptyline, imipramine, and trimipramine), Antipsychotics e.g., clozapine, quetiapine
- **First-generation antihistamines** (e.g., promethazine, dimenhydrinate)

Features

- Dry mouth, warm, flushed skin, thirst, urinary retention, tachycardia, arrhythmias, mydriasis, confusion, and agitation
- "Red" (cutaneous vasodilation), "Dry" (anhidrosis), "Hot" (anhidrotic hyperthermia), "Blind" (nonreactive mydriasis), "Full" (urinary retention) and "Mad" (delirium, hallucinations).

Diagnosis

- Clinical findings and history of exposure
- ECG: to rule out QRS, QTc interval prolongation, and other arrhythmias

Treatment: Supportive treatment

- **Hyperthermia:** Rapid cooling
- **Agitation and seizures:** benzodiazepines
- **GI decontamination:** activated charcoal (AC; 1 g/kg, maximum 50 g)
- **Antidote for purely anticholinergic poisoning (e.g. atropine):** physostigmine. Physostigmine is contraindicated in tricyclic antidepressant overdose, even in the case of severe anticholinergic symptoms, because it can cause cardiac arrest.

Dystonia

Definition: Involuntary sustained or spasmodic muscle contractions

Types

- **Focal dystonia:** Involves a single body part
  - ⇨ **Cervical dystonia (torticollis)** is the most common focal dystonia.
  - ⇨ **Blepharospasm**: a sustained eyelid twitch (associated with stress, lack of sleep, nutrition, and strain).
  - ⇨ **Writer's cramp dystonia** → hyperextension or hyperflexion of the wrist and fingers → **unable to write.** may be **triggered by** repetitive activities such as writing and attempting to play the piano or other musical instruments. Often **relieved by** a geste antagoniste, (in which palpation of another unaffected part of the body leads to relief of symptoms)
- **Segmental dystonia:** Affects 2 or more contiguous regions of the body
- **Generalised dystonia**: involves trunk and limbs.

Management

- **Treatment of underlying cause** (e.g., cessation of the causative drug)
- **Anticholinergic agents**
  - ⇨ Procyclidine (IV, IM: 5 mg, oral: 2.5 mg 3 times daily)
  - ⇨ Benztropine (IV, IM, oral: 1 to 2 mg 2 to 3 times daily)
- **Focal dystonia, e.g. cervical dystonia (torticollis):** botulinum toxin injections (inhibits the release of acetylcholine at the neuromuscular junction, resulting in flaccid paralysis.)

> **Most cases of acute dystonia are caused by antipsychotic drugs.**

Oculogyric crisis

Definition:
an episode of spasmodic upward movement of the eyes that typically lasts for several minutes.

Causes
- Phenothiazines (chlorpromazine, fluphenazine, perphenazine, prochlorperazine
- Neuroleptic drugs (Usually typical neuroleptic drugs such as haloperidol or chlorpromazine, but is unusual with newer agents such as olanzapine or clozapine)
- Other dopamine antagonists, e.g. Metoclopramide
- Basal ganglia disorders (e.g., postencephalitic Parkinsonism, Parkinson's disease)

Management: Anticholinergic agents
- Procyclidine (IV, IM: 5 mg, oral: 2.5 mg 3 times daily)
- Benztropine (IV, IM, oral: 1 to 2 mg 2 to 3 times daily)

Botulinum toxin type A (or trade name Botox®)

Definition
Action: a toxin produced from Clostridium botulinum bacteria → block acetylcholine release at the neuromuscular junction → muscle weakness.

Indications:
the treatment of choice for focal dystonia such as cervical dystonia (torticollis), blepharospasm and hemi-facial spasm.

Side effects
- Excessive weakness in the treated muscle (the main side-effect)
- Systemic absorption can affect distal muscles causing symptoms such as diplopia and dysphagia.

Contra-indications
- Myasthenia gravis and other generalised muscle conditions

Botulism

Definition

- A lethal neuroparalytic condition characterized by symmetric flaccid paralysis and mental status changes after an ingestion of a neurotoxin toxin produced by Clostridium Botulinum bacteria.

Pathophysiology

- **Ingestion of toxin (types A, B, and E) produced by Clostridium Botulinum** (a gram-positive rod, spore-forming, obligate anaerobe, produces heat-labile neurotoxin) (**typically from home-canned foods) → inhibition of acetylcholine release at the neuromuscular junction** → symmetric **flaccid paralysis**

Features

- **Descending paralysis:** Diplopia, Ptosis, Facial weakness, Dysarthria, and Dysphagia, respiratory difficulty and flaccid limb weakness with depressed or absent reflexes.
- **Autonomic features: fixed dilated pupils**, dry mouth, paralytic ileus and bradycardia.
- **Gastrointestinal symptoms:** nausea, and vomiting, later followed by constipation (only present in 30% of cases of foodborne botulism; absent in wound botulism)

Investigations

- It is a neuromuscular junction disorder and therefore nerve conduction studies and EMG are normal.
- Cerebrospinal fluid analysis is usually normal.
- Repetitive nerve stimulation shows incremental responses, which is diagnostic of botulism.
- sensation is normal

Treatment

- **Heptavalent antitoxin is the most appropriate therapy**

> **4 D's of botulism: Dysarthria, Diplopia, Dysphagia, and Dyspnea.**

Parkinson Plus syndromes

Definition

- Parkinson plus syndromes are neurodegenerative disorders that share features of Parkinson's disease (PD) but have additional neurological signs indicating broader neurodegeneration.

Comparison table for Parkinson plus syndromes:

Feature	Progressive Supranuclear Palsy (PSP)	Multiple System Atrophy (MSA)	Corticobasal Degeneration (CBD)	Dementia with Lewy Bodies (DLB)
Key Features	Early postural instability, vertical gaze palsy, axial rigidity, speech and swallowing difficulties	Autonomic dysfunction (e.g., orthostatic hypotension, urinary incontinence), cerebellar signs, poor levodopa response	Asymmetric rigidity, dystonia, limb apraxia, cortical sensory deficits, alien limb phenomenon	Early cognitive decline, visual hallucinations, REM sleep behavior disorder, fluctuating alertness, parkinsonian features
Pathophysiology	Tau protein accumulation affecting the brainstem and basal ganglia	Alpha-synuclein accumulation in the basal ganglia, cerebellum, and brainstem	Tau protein accumulation in cortical and basal ganglia regions	Widespread Lewy body (alpha-synuclein) deposition in cortical and subcortical areas
Response to Levodopa	Poor or transient response	Limited efficacy	Minimal or no response	Modest response
Distinctive Clinical Signs	Vertical gaze palsy, early falls	Autonomic symptoms, cerebellar ataxia, poor levodopa response	Limb apraxia, alien limb phenomenon	Prominent cognitive impairment and visual hallucinations early in the disease
Imaging Findings	Midbrain atrophy (**"hummingbird sign"**)	Pontocerebellar atrophy, putaminal slit	Cortical and subcortical atrophy	General cortical atrophy and Lewy body presence (via specialized imaging)
Progression	Rapid (6–10 years median survival)	Rapid (6–10 years median survival)	Gradual but severe disability	Variable, often progressive cognitive and motor decline
Complications	Severe disability, aspiration pneumonia, frequent falls	Severe autonomic dysfunction, cardiovascular instability	Progressive motor dysfunction, limb apraxia	Cognitive decline, increased risk of falls and injuries, aspiration

Feature	Progressive Supranuclear Palsy (PSP)	Multiple System Atrophy (MSA)	Corticobasal Degeneration (CBD)	Dementia with Lewy Bodies (DLB)
Supportive Treatments	Symptom management with physiotherapy, speech therapy, and adaptive devices	Lifestyle modifications, physiotherapy, autonomic support	Supportive care for rigidity and apraxia, physical and occupational therapy	Cognitive and supportive therapies, safety measures for fall prevention

Progressive supranuclear palsy: a triad of parkinsonism, vertical gaze palsy and cognitive impairment

Multiple system atrophy : a triad of

- **Parkinsonism**
- **Autonomic disturbance (atonic bladder, postural hypotension)**
- **Cerebellar signs (e.g., ataxia, tremor, dysarthria)**

Differential diagnoses of Parkinson-plus syndromes			
Multiple system atrophy	**Progressive supranuclear palsy**	**Corticobasal degeneration**	**Dementia with Lewy bodies**
• **Autonomic dysfunction with urogenital problems**	• **Vertical gaze palsy** • Frontal lobe disturbances	• Asymmetric motor symptoms • **Alien limb phenomenon**	• Lewy bodies • **Visual hallucinations**

Normal pressure hydrocephalus (NPH)

Category	Details
Definition	Reversible cause of dementia seen in elderly patients.
Mechanism	- Secondary to reduced CSF absorption at the arachnoid villi. - ↓ CSF absorption → CSF accumulation → enlargement of the ventricles.
Causes	- Idiopathic (most common in adults > 60 years). - Secondary causes: head injury, subarachnoid haemorrhage, meningitis.
Key Features (Triad)	1. Urinary incontinence. 2. Dementia and bradyphrenia. 3. Gait abnormality (similar to Parkinson's disease).
Diagnosis	- **Imaging**: MRI (initial test), CT. → Ventriculomegaly without sulcal enlargement. → Enlarged fourth ventricle. - **CSF Tap Test**: Confirmatory test. → Opening pressure: normal/slightly elevated. → Symptom improvement after CSF removal confirms NPH. → Lumbar puncture is both diagnostic and therapeutic.
Management	- **Initial Steps**: CSF drainage via repeated lumbar puncture. - **Definitive Treatment**: Ventriculo-peritoneal shunting.

Normal pressure hydrocephalus

- Classic triad of **urinary incontinence, dementia, and gait apraxia.**

Dementia

Common Causes of Dementia

- **Alzheimer's Disease**: >50% of dementia cases.
- **Multi-Infarct Dementia**: Due to cerebrovascular disease (20% of cases).
- **Lewy Body Dementia**: 10-20% of cases.

Rarer Causes of Dementia (5% of cases)

- **Huntington's Disease**
- **Creutzfeldt-Jakob Disease (CJD)**
- **Pick's Disease**: Frontal and temporal lobe atrophy.
- **HIV**: Dementia in ~50% of AIDS patients.

Features of Dementia

- **Cognitive Impairment**: Assessed by Mini-Mental State Examination (MMSE); score <24 suggests dementia.
- **Short-Term Memory Loss**: Common in Alzheimer's disease.
- **Long-Term Memory**: Usually preserved in early stages.
- **Orientation**: Generally preserved initially, but declines in advanced stages.

Distinguishing Dementia from Normal Aging

- **Normal Aging**: Minor memory issues, occasional word-finding difficulty, slower processing but preserved daily functioning and independence.
- **Dementia**: Noticeable impairment affecting daily activities and independence. Alzheimer's disease may also show behavioral changes (e.g., aggression, depression).

Types of Dementia

1. **Alzheimer's Disease (AD)**
   - Progressive degeneration primarily affecting temporal and parietal lobes.
   - **Key Pathology**: Amyloid plaques, neurofibrillary tangles (tau protein).
   - **Features**: Memory loss, language difficulties, spatial navigation issues.
   - **Genetics**: Early-onset cases linked to PSEN1 and APP genes.
2. **Lewy Body Dementia (LBD)**
   - Characterized by Lewy bodies (alpha-synuclein inclusions) in cortical neurons.
   - **Features**: Visual hallucinations, parkinsonism, cognitive fluctuations, **sensitivity to neuroleptics**.
   - **Differential Diagnosis**: Lewy body dementia if motor and cognitive symptoms appear within 1 year; otherwise, Parkinson's disease dementia.
3. **Frontotemporal Dementia (FTD)**
   - Degeneration of frontal and temporal cortices; includes Pick's disease.
   - **Types**:
     - **Frontotemporal Dementia**: Personality and behavioral changes.
     - **Progressive Non-Fluent Aphasia**: Non-fluent, agrammatic speech.
     - **Semantic Dementia**: Fluent but empty speech, poor meaning retention.
   - **Features**: Early-onset (usually <65), preserved memory, personality changes.
4. **Vascular Dementia**
   - Caused by cerebrovascular disease leading to brain ischemia.

- **Features**: Stepwise progression, focus on managing vascular risk factors.

Investigations

- **Routine Labs**: Exclude reversible causes (e.g., hypothyroidism, vitamin B12 deficiency).
- **Neuroimaging**:
  - **MRI/CT**: Assess for structural brain changes; MRI preferred.
  - **SPECT/PET**: Differentiates dementia types (e.g., Alzheimer's, vascular, frontotemporal).
  - **CSF Analysis**: For rapid-progressing dementias like CJD; amyloid and tau markers can help diagnose Alzheimer's.

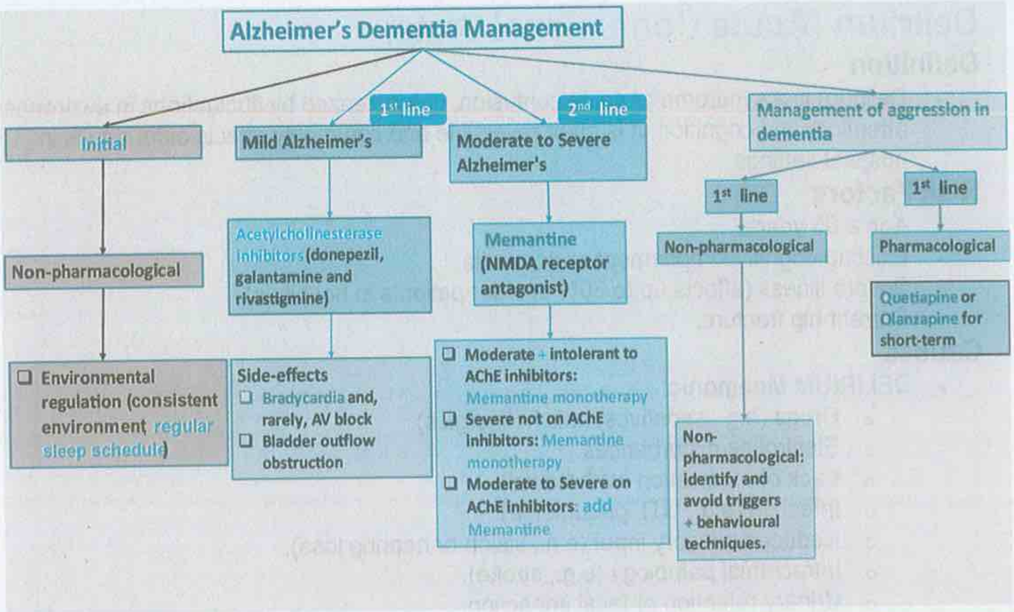
Management

Non-Pharmacological

- **Cognitive Therapy**: Memory exercises, structured routines.
- **Environmental Modifications**: Regular sleep schedule, familiar surroundings to help orientation.
- **Behavioral Interventions**: For aggression or agitation, avoid pharmacological interventions if possible.

Pharmacological Treatment

1. **Alzheimer's Disease**:
   - **Mild to Moderate**: Acetylcholinesterase inhibitors (Donepezil 5-10 mg/day, Rivastigmine 3-6 mg BID, Galantamine 8-24 mg/day).
   - **Moderate to Severe: Memantine** (10-20 mg/day).
   - **Considerations**: Discontinue cholinesterase inhibitors when MMSE <12; memantine may be continued in severe cases.
2. **Lewy Body Dementia**:
   - **First-Line**: Rivastigmine, especially for hallucinations and cognitive symptoms.
   - **Avoid Antipsychotics**: High sensitivity to neuroleptics; quetiapine at low doses may be used if necessary.
3. **Frontotemporal Dementia**:
   - No specific medications; treat behavioral symptoms (e.g., SSRIs for mood/behavioral disturbances).
4. **Vascular Dementia**:
   - Manage vascular risk factors (e.g., antihypertensives, antiplatelets) to prevent further decline.



Haloperidol is contra-indicated in Lewy body dementia

SPECT scan is most likely test to confirm the diagnosis of Lewy body dementia **(memory impairment, hallucinations, resting tremor, festinating gait and an expressionless face)**

Parkinsonian symptoms + agitation. deteriorated after prescribing haloperidol. Lewy body dementia

Patients with Frontotemporal lobar degeneration display changes of personality and social behavior, but their memory generally remains intact.

Presence of the e4 allele of apo-lipoprotein E → Alzheimer's disease
Loss of GABA is seen in → Parkinson's disease.
Peri-vascular mononuclear inflammation is seen in → multiple sclerosis.
Loss of Betz cells is seen in → motor neurone disease.

Lewy body dementia: a triad of: Dementia, parkinsonism, and visual hallucinations

Delirium (Acute Confusional State)

Definition

- Delirium is a syndrome of acute confusion, characterized by fluctuations in awareness, attention, and cognition. It is often reversible and commonly affects older adults in hospital settings.

Risk Factors

- Age ≥ 65 years.
- Existing cognitive impairment or dementia.
- Severe illness (affects up to 30% of older patients in hospitals).
- Current hip fracture.

Causes

- **DELIRIUM Mnemonic**:
  - **D**rugs (e.g., sedatives, anticholinergics).
  - **E**lectrolyte disturbances.
  - **L**ack of medication (withdrawal).
  - **I**nfection (e.g., UTI, pneumonia).
  - **R**educed sensory input (e.g., vision or hearing loss).
  - **I**ntracranial pathology (e.g., stroke).
  - **U**rinary retention or fecal impaction.
  - **M**yocardial or pulmonary disease.

Clinical Features

- **Cognitive Impairment**: Poor concentration, confusion, memory disturbances (short-term > long-term).
- **Perception**: Visual or auditory hallucinations.
- **Physical Function**: Reduced mobility, restlessness, agitation, sleep disturbances.
- **Behavior**: Social withdrawal, mood changes, lack of cooperation.

Diagnosis

- **Confusion Assessment Method (CAM)**: Primary tool for delirium diagnosis.
- If unsure whether symptoms are due to delirium, dementia, or both, treat for delirium first.

Management

- **Identify and Treat Underlying Cause**: Address infections, correct metabolic disturbances, or withdraw offending drugs.
- **Non-Pharmacological Management**:
  - Environmental adjustments (e.g., adequate lighting, quiet environment).
  - Verbal and non-verbal de-escalation techniques.
  - Involve family members for reassurance.
- **Pharmacological Management** (for severe agitation unresponsive to non-pharmacological approaches):
  - **Haloperidol**: Short-term use recommended by NICE, with a typical starting dose of **0.5 mg**, titrated as needed (usually up to 1-2 mg daily, not exceeding 5 mg/day). Limit use to ≤1 week.
  - **Avoid in Lewy Body Dementia or Parkinson's Disease**: These patients are sensitive to antipsychotics.

Reassessment

- If delirium persists, re-evaluate for potential undiagnosed underlying causes or assess for possible coexisting dementia.

Creutzfeldt-Jakob disease (CJD)

Definition

- Creutzfeldt-Jakob disease (CJD) is a rapidly progressive neurological disorder caused by prions—misfolded proteins that resist degradation and induce misfolding of other proteins, leading to neurodegeneration.

Epidemiology

- CJD is the most common prion disease in humans.

Causes and Types

- **Sporadic CJD** (~85%): No identifiable cause, often in middle-aged individuals.
- **Familial CJD** (~10–15%): Genetic mutations in the PRNP gene.
- **Acquired CJD** (<1%):
  - **Iatrogenic CJD**: Transmission through medical procedures (e.g., organ transplantation, blood transfusion).
  - **Variant CJD (vCJD)**: Caused by ingestion of beef infected with bovine spongiform encephalopathy (BSE).

Pathophysiology

- Normal cellular prion proteins (PrPc) misfold into prions (PrPSc) with increased beta-pleated sheet structure. These prions accumulate, forming plaques and causing neuronal cell death, leading to spongiform encephalopathy.

Clinical Features

- **Rapidly Progressive Dementia**: Typically develops over weeks to months.
- **Myoclonus**
- **Cerebellar Signs**: Gait instability, ataxia.
- **Pyramidal Weakness**
- **Behavioral Abnormalities**
- **Akinetic Mutism**

Types of CJD

Form	Features
Sporadic	Accounts for ~85% of cases, **average onset age of 65**, median disease duration 5 months, rapid progression.
Genetic	PRNP gene mutation, may occur at younger ages, family history often negative, disease duration several years.
Iatrogenic	Transmission through invasive medical treatments, similar to sporadic CJD in presentation.
Variant (vCJD)	**Median age of onset ~25 years**, initial psychological symptoms (e.g., anxiety, withdrawal), followed by ataxia and myoclonus. EEG often normal, MRI shows bilateral pulvinar high signals. Disease duration ~13 months.

Investigations

- **CSF Analysis**: Elevated 14-3-3 protein, especially useful in sporadic CJD.
- **MRI**: Hyperintense signals in caudate nucleus, putamen, or two cortical regions (temporal, parietal, occipital) for sporadic CJD; bilateral pulvinar high signals for vCJD.
- **EEG**:
  - Sporadic CJD: Biphasic, high-amplitude sharp waves.
  - Variant CJD: Usually normal.
- **Brain Biopsy**: Definitive diagnosis showing spongiform degeneration and amyloid plaques in vCJD.

Treatment

- No curative treatment available; management is symptomatic and includes palliative care in advanced stages.

Rapidly progressive dementia and myoclonic jerks are the hallmarks of Creutzfeldt-Jakob disease.

Following disease manifestation, most individuals with sporadic CJD die within 12 months, usually from complications such as pneumonia.

Transient global amnesia

Definition

- Transient, isolated loss of memory function without lasting cognitive impairment.

Pathophysiology

- Exact cause unknown; thought to result from transient ischemia affecting the thalamus, particularly the amygdala and hippocampus.

Risk Factors

- Commonly affects individuals over 50 years old.
- Triggered by psychological or physical stress.

Diagnostic Criteria

- Sudden onset of amnesia (anterograde or partial retrograde).
- Patient may repeatedly ask the same questions, appearing anxious.
- Episode duration: 1–24 hours (never exceeds 24 hours).
- Disorientation in time and place, but personal identity remains intact.
- Normal perception and no other cognitive or neurological deficits.
- No memory of the events following the attack.

Investigations

- If diagnosis is clear, no further tests are necessary.
- If diagnosis is uncertain:
  - **MRI**: May show focal hyperintense lesions in the hippocampus.
  - **EEG**: To rule out epilepsy or other causes of amnesia.

Differential Diagnosis

- **Transient Epileptic Amnesia:**
  - Shorter duration (<1 hour), multiple episodes, often occurring upon waking.
  - Accompanied by typical epileptic signs (e.g., motor automatism, limb shaking).

Management

- **Observation until symptoms resolve; no specific treatment required.**
- Imaging only if amnesia persists beyond 24 hours.

Prognosis

- Spontaneous resolution within 24 hours.
- Recurrence is rare.

Restless legs syndrome (RLS)

Definition

- RLS is characterized by spontaneous, continuous movements of the lower limbs often associated with paraesthesia.

Epidemiology

- Affects 2-10% of the population.
- Equally prevalent in males and females; familial cases in up to 77%.

Pathophysiology

- Abnormal dopamine pathways and iron deficiency in the substantia nigra are key mechanisms.

Clinical Features

- **Primary Symptoms**:
  - Uncontrollable urge to move the legs (akathisia), initially worse at night but may progress to daytime.
  - Movements may be noted as **Periodic Limb Movements of Sleep (PLMS)**.
  - Symptoms start or worsen during rest and improve with movement.
- **Sensory Symptoms**:
  - Paraesthesias described as crawling or throbbing sensations.

Investigations

- **Initial Test**: Iron studies to check for deficiency.
- **Polysomnogram**: To quantify PLMS if needed.

Causes

- **Primary**: Idiopathic, often familial.
- **Secondary**:
  - **Chronic Conditions**: Iron deficiency (with or without anemia), vitamin deficiencies.
  - **Drugs**: H1 antihistamines, antidepressants, dopamine antagonists (e.g., neuroleptics, metoclopramide), lithium, beta blockers.
  - **Pregnancy**: Common temporary trigger.

Diagnosis Criteria (International Restless Legs Syndrome Study Group)

1. Urge to move limbs, often with paraesthesias.
2. Symptoms worsen during rest and are partially relieved by movement
3. Motor restlessness.
4. Nocturnal symptom exacerbation.

- **Note**: Exclude iron deficiency anemia in the diagnostic workup.

Management

- **Lifestyle Modifications**:
  - Avoid evening stimulants (caffeine, tobacco, alcohol).
  - Regular exercise (avoid close to bedtime).
  - Simple relief measures: walking, stretching, massage.
- **Treat Underlying Causes**:
  - Correct iron deficiency if present.
- **Pharmacological Treatment**:
  - **1st Line**: Pregabalin, gabapentin, or dopamine agonists (e.g., ropinirole, pramipexole, rotigotine skin patch).

> **A low serum ferritin is most likely to be a cause of secondary restless legs syndrome**

Essential tremor

Definition

- Essential tremor (ET) is a common neurological disorder characterized by an action tremor, primarily affecting the hands and arms, but can also involve the head and voice. It is distinct from rest tremors seen in Parkinson's disease.

Epidemiology

- Most common movement disorder.
- Often hereditary (autosomal dominant pattern).
- Can affect individuals of all ages but is more common in people over 40.

Features

- **Tremor Characteristics**:
  - Bilateral, often symmetric, action or postural tremor (e.g., occurs when holding objects or performing tasks).
  - Tremor can worsen with stress, caffeine, or fatigue.
- **Locations**:
  - Primarily hands and arms, but may include head and voice.
- **Absence of Other Neurological Signs**:
  - No rigidity, bradykinesia, or postural instability as seen in Parkinson's disease.

Diagnosis

- **Clinical Diagnosis**: Based on the history and physical examination.
- **Differentiation**:
  - Rule out Parkinson's disease and other movement disorders.
  - Family history can support diagnosis.

Investigations

- Generally, no specific tests are required unless other conditions are suspected.
- **Thyroid function tests**: To exclude hyperthyroidism if indicated.
- **Imaging**: Not typically required unless other neurological disorders are suspected.

Management

- **Lifestyle Modifications**:
  - Avoid triggers (e.g., caffeine, stress).
- **Pharmacological Treatment**:
  - **1st Line**:
    - **Propranolol**: Start with 40-60 mg orally twice daily, may increase to 120-320 mg/day as needed.
    - **Primidone**: Start with 25 mg at night, gradually increase to 250 mg/day in divided doses.
  - **2nd Line**:
    - **Topiramate**: 25-50 mg/day, can be increased to 200-400 mg/day.
    - **Gabapentin**: 300-1,800 mg/day in divided doses.
- **Severe Cases**:
  - **Botulinum Toxin Injections**: For head or voice tremors.
  - **Surgical Options**:
    - **Deep Brain Stimulation (DBS)**: Targeting the thalamus for refractory cases.

Prognosis

- ET is a chronic condition with a variable course.
- Tremor severity can increase over time, but it generally does not lead to other neurological impairments.

Consider an essential tremor in a patient presenting with chronic bilateral hand tremors without further neurological deficits and positive family history.

Holmes tremor

Definition

- Holmes tremor, also known as rubral tremor or midbrain tremor, is a low-frequency, complex tremor that typically combines resting, postural, and action tremor components.

Pathophysiology

- Often associated with lesions affecting the **midbrain**, **thalamus**, or **cerebellar outflow pathways**.
- Commonly linked to structural damage from **stroke**, **trauma**, **multiple sclerosis**, or tumors.
- The delayed onset of weeks to months after the causative brain injury is characteristic.

Features

- **Combination Tremor**: Involves resting, postural, and intention tremor components.
- **Frequency**: Typically <4.5 Hz (**low frequency**).
- **Amplitude**: Can be severe and disabling.
- **Location**: Usually unilateral, affecting one side of the body.

Diagnosis

- **Clinical Assessment**: Based on patient history, neurological examination, and identifying any underlying structural lesion.
- **Imaging**:
  - **MRI**: To detect midbrain, thalamic, or cerebellar lesions.
- **Differentiation**: Distinguish from other tremor types by its combination of rest and action tremor features.

Management

- **Pharmacological Treatment**:
  - **Levodopa**: Starting dose 100-200 mg/day, can be titrated based on response.
  - **Clonazepam**: 0.5-1 mg/day to reduce tremor amplitude.
  - **Gabapentin**: Starting at 300 mg/day, titrated up to 1,800 mg/day in divided doses.
- **Other Medications**: Dopamine agonists and beta-blockers may provide partial relief in some cases.
- **Surgical Options**:
  - **Deep Brain Stimulation (DBS)**: Targeting the thalamus or globus pallidus for severe, refractory cases.
  - **Thalamotomy**: Rarely performed but considered in certain cases.

Prognosis

- Holmes tremor is generally chronic and may be persistent, depending on the underlying cause.
- Early identification and management can help mitigate functional impairment, but complete resolution is rare.

Holmes tremor → lesion in the red nucleus

Holmes tremor is a **low-frequency**, **irregular tremor present at rest, posture, and action,** often caused by brainstem or thalamic lesions.
In contrast, **Parkinsonian resting tremor** is a **rhythmic**, **high-frequency tremor typically present at rest**, **suppressed by voluntary movement**, and associated with other parkinsonian features like bradykinesia and rigidity.

Friedreich's Ataxia and Ataxic Telangiectasia

Feature	Friedreich's Ataxia (FA)	Ataxic Telangiectasia (AT)
Definition	An autosomal recessive neurodegenerative disorder characterized by progressive ataxia and systemic involvement.	An autosomal recessive disorder characterized by progressive ataxia, immunodeficiency, and telangiectasias.
Genetics	Caused by mutations in the **FXN gene** on chromosome 9 leading to reduced frataxin protein.	Caused by mutations in the **ATM gene** on chromosome 11, which encodes a protein involved in DNA repair.
Age of Onset	Typically presents in childhood, around 5-15 years of age.	Usually presents early in childhood, often before age 5.
Clinical Features	- **Progressive gait ataxia**. - **Dysarthria** (slurred speech). - **Muscle weakness** and **loss of reflexes** in the lower limbs. - **Scoliosis**. - **Cardiomyopathy** and diabetes mellitus are common.	- **Progressive cerebellar ataxia**. - **Oculocutaneous telangiectasias** (small, red dilated blood vessels on eyes and skin). - **Frequent infections** due to immunodeficiency. - **Increased risk of malignancies**, particularly lymphomas and leukemias. - Delayed physical and sexual development.
Neurological Findings	- **Loss of proprioception** and vibration sense. - **Absent deep tendon reflexes** (especially lower limbs).	- **Cerebellar signs** (e.g., ataxic gait, dysmetria). - **Oculomotor apraxia** (difficulty with voluntary eye movement).
Systemic Involvement	- **Cardiac**: Hypertrophic cardiomyopathy. - **Endocrine**: Diabetes mellitus may develop.	- **Immune**: Deficiency leading to recurrent sinopulmonary infections. - **Skin**: Telangiectasias on the conjunctiva and other body parts.
Genetic Testing	**GAA trinucleotide repeat expansion** in the FXN gene confirms diagnosis.	**ATM gene mutation analysis** confirms diagnosis.
Investigations	- **MRI**: Atrophy of the spinal cord and cerebellum. - **Nerve conduction studies**: Sensory neuropathy.	- **MRI**: Cerebellar atrophy. - **Immunological tests**: Low levels of IgA, IgG, or IgE.

Management	- **Supportive care**: Physical therapy, orthopedic interventions for scoliosis. - **Cardiac monitoring** and management for cardiomyopathy. - **Antioxidants** and experimental treatments targeting mitochondrial function.	- **Supportive care**: Management of infections, immunoglobulin replacement therapy. - **Cancer surveillance**: Regular screening due to high malignancy risk. - **Physical therapy** and symptomatic treatment for ataxia.
Prognosis	Progressive with life expectancy into early adulthood; cardiac disease is a major contributor to mortality.	Progressive, with most patients surviving into their second or third decade; high cancer risk and recurrent infections impact prognosis.

Friedreich's ataxia versus Ataxia-telangiectasia

	Friedreich's ataxia	Ataxia-telangiectasia
Epidemiology	The most common autosomal recessive ataxia in children	The second most common autosomal recessive ataxia in children, after Friedreich's ataxia
Affected chromosome	Chromosome 9	Chromosome 11
Affected gene	FXN gene	ATM gene
Age of presentation	Late childhood (10-15 years old)	Early childhood (1 – 5 years old)
Similarities	▪ Autosomal recessive ▪ cerebellar ataxia ▪ onset in childhood	▪ Autosomal recessive ▪ Cerebellar ataxia ▪ Onset in childhood
Associations	Kyphoscoliosis and pes cavus (high-arched palate)	Immunodeficiency & risk of developing malignancy
Cause of death	Hypertrophic cardiomyopathy (HCM)	Bronchiectasis or malignancy
Average life expectancy	37 years	25 years

The 6 A's of ataxia-telangiectasia: ATM gene, Ataxia, spider Angiomas, IgA deficiency, Alpha-fetoprotein elevation, and Avoid X-ray procedure (due to increased risk of malignancies)

Motor neuron disease (MND)

Definition

- A group of progressive neurodegenerative disorders characterized by the selective loss of motor neurons, leading to muscle weakness, wasting, and eventual paralysis. Amyotrophic lateral sclerosis (ALS) is the most common type.

Pathophysiology

- Involves degeneration of both **upper motor neurons (UMNs)** and **lower motor neurons (LMNs)**.
- Pathological hallmark includes the presence of **ubiquitin-positive inclusions** and **TDP-43 protein aggregates** in affected neurons.

Types of MND

- **Amyotrophic Lateral Sclerosis (ALS)**: The most common form, affecting both UMNs and LMNs.
- **Progressive Bulbar Palsy (PBP)**: Affects LMNs in the brainstem, leading to difficulties in speech and swallowing.
- **Progressive Muscular Atrophy (PMA)**: Affects primarily LMNs.
- **Primary Lateral Sclerosis (PLS)**: Affects primarily UMNs; less common and slower progression.

Epidemiology

- Typically presents in middle to late adulthood (average onset between 50-70 years).
- Slight male predominance.
- Familial cases occur in about 5-10% of patients and are often linked to mutations in **SOD1**, **C9orf72**, and other genes.

Clinical Features

- **General Signs**:
  - **UMN Signs**: Spasticity, hyperreflexia, muscle stiffness.
  - **LMN Signs**: Muscle weakness, atrophy, fasciculations.
- **Specific Presentations**:
  - **ALS**: Weakness in the limbs, dysarthria, dysphagia, muscle cramps.
  - **PBP**: Bulbar symptoms (speech and swallowing difficulties).
  - **PMA**: Progressive weakness and atrophy, starting distally.
  - **PLS**: Progressive spasticity and stiffness.
- **Cognitive Impairment**: Some patients develop frontotemporal dementia (FTD).

Investigations

- **Clinical Diagnosis**: Based on history and neurological examination.
- **Electromyography (EMG)**: Confirms LMN involvement by showing signs of denervation and reinnervation.
- **MRI**: To rule out other conditions (e.g., spinal cord compression, multiple sclerosis).
- **Genetic Testing**: For familial MND and when hereditary forms are suspected.

Management

- **No cure**; treatment focuses on symptom relief and supportive care.
- **Riluzole**: Prolongs survival by 2-3 months (50 mg twice daily).
- **Edaravone**: May slow disease progression in some patients.
- **Symptomatic Treatment**:
  - **Spasticity**: Baclofen or tizanidine.
  - **Sialorrhea (excessive saliva)**: Anticholinergic drugs like glycopyrrolate.
  - **Dysphagia**: Speech and swallow therapy, gastrostomy for feeding.

- **Respiratory Support**: Non-invasive ventilation (e.g., BiPAP) to improve quality of life and prolong survival.
- **Multidisciplinary Approach**: Involves neurologists, physiotherapists, occupational therapists, and palliative care specialists.

Prognosis

- **Progressive and fatal**. Median survival for ALS is 3-5 years post-diagnosis, with respiratory failure being the most common cause of death.
- **Slower progression** in PLS and some genetic subtypes.

Progressive motor weakness and pseudo-bulbar palsy + normal sensations + normal brain imaging → always think of amyotrophic lateral sclerosis.
Electromyography is the best investigation to carry out next.

Motor neuron disease - treatment: NIV is better than riluzole

Headache, neuro infections, tumours, Genetics and inflammatory disorders

Headache

Headache Requiring Further Investigation or Referral

- **Red Flags:**
    1. Worsening headache with fever.
    2. Sudden-onset headache reaching maximum intensity within 5 minutes.
    3. New-onset neurological deficit or cognitive dysfunction.
    4. Change in personality or impaired consciousness.
    5. Recent head trauma (within 3 months).
    6. Headache triggered by cough, Valsalva manoeuvre, or exercise.
    7. Orthostatic headache (changes with posture).
    8. Symptoms indicative of giant cell arteritis or acute narrow-angle glaucoma.
    9. Substantial change in headache characteristics.
    10. New-onset headache with compromised immunity or a history of malignancy.
    11. Unexplained vomiting.

Types and Features of Common Headaches

Feature	Tension-Type Headache	Migraine (with/without Aura)	Cluster Headache
Pain Location	Bilateral	Unilateral or bilateral	Unilateral (around eye/side of face)
Pain Quality	Pressing/tightening	Pulsating	Sharp, boring, or throbbing
Pain Intensity	Mild to moderate	Moderate to severe	Severe to very severe
Effect on Activities	Not aggravated by daily activities	Aggravated by routine activities	Causes restlessness/agitation
Other Symptoms	None	Light/sound sensitivity, nausea, visual aura (reversible, lasting 5-60 mins)	Red/watery eye, nasal congestion, ptosis, miosis
Duration	30 minutes to continuous	4-72 hours (adults)	15-180 minutes

Cluster Headache

- **Epidemiology**: More common in men, smokers, and younger males (<40).
- **Features**: Intense pain around one eye, recurrent episodes (15 mins-2 hours), often nocturnal.
- **Management**:
    - **Acute**: 100% oxygen (≥12 L/min), subcutaneous/nasal triptan.
    - **Prophylaxis**: Verapamil, prednisolone; consider neurologist referral for imaging.
- **Differential**: Distinguish from chronic paroxysmal hemicrania (responds to indomethacin).

Migraine

- **Diagnostic Criteria**:
  - **Attacks**: ≥5 fulfilling specific criteria (4-72 hours, unilateral, pulsating, aggravated by activities).
  - **Associated Symptoms**: Nausea, photophobia, phonophobia.
- **Management**:
  - **Acute**: Oral triptan + NSAID/paracetamol.
  - **Prophylaxis**: Propranolol, topiramate, amitriptyline (consider patient comorbidities).
  - **Special Notes**: Avoid combined oral contraceptive pills in migraine with aura (stroke risk).

Idiopathic Intracranial Hypertension (IIH)

- **Risk Factors**: Young, obese females; certain medications.
- **Features**: Chronic postural headache, blurred vision, papilloedema, sixth nerve palsy.
- **Diagnosis**: Elevated CSF pressure (>20 cm H_2O), normal CSF composition.
- **Management**: Weight loss, acetazolamide, possible surgical intervention (e.g., LP shunt).

Medication Overuse Headache

- **Definition**: Headache ≥15 days/month due to overuse of headache medication for >3 months.
- **Management**: Abrupt withdrawal of simple analgesics and triptans; gradual withdrawal for opioids.

Post-Lumbar Puncture Headache

- **Features**: Worsens when upright, improves when recumbent, develops 24-48 hours post-LP.
- **Management**: Supportive, possible blood patch if persistent >72 hours.

Diagnosis and treatment for common types of headaches

Type	Diagnostic Criteria	Treatment with Drug Doses
Tension-Type Headache	- Bilateral pain, pressing/tightening quality, mild to moderate intensity. - Not aggravated by routine activities. - No nausea or vomiting; may have photophobia or phonophobia (not both).	- **Paracetamol**: 500-1,000 mg every 4-6 hours, max 4,000 mg/day. - **Ibuprofen**: 200-400 mg every 4-6 hours, max 1,200 mg/day. - Stress management and lifestyle changes.

Type	Diagnostic Criteria	Treatment with Drug Doses
Migraine (without Aura)	- ≥5 attacks lasting 4-72 hours. - Unilateral, pulsating, moderate/severe intensity, aggravated by activities. - Accompanied by nausea/vomiting or photophobia/phonophobia.	- **Acute**: **Sumatriptan**: 50-100 mg orally, max 200 mg/day. **Rizatriptan**: 5-10 mg orally, max 30 mg/day. - **Prophylaxis**: **Propranolol**: 40-160 mg/day in divided doses. **Topiramate**: Start at 25 mg/day, increase to 50-100 mg/day. **Amitriptyline**: 10-25 mg at night, increase as needed.
Migraine (with Aura)	- Reversible visual, sensory, or speech symptoms developing over ≥5 minutes, lasting 5-60 minutes. - Followed by a headache meeting migraine without aura criteria.	- **Acute**: Same as migraine without aura. - **Prophylaxis**: Similar to migraine without aura but avoid combined oral contraceptives due to stroke risk.
Cluster Headache	- Severe, unilateral orbital or temporal pain lasting 15-180 minutes. - Occurs 1-8 times/day, associated with conjunctival injection, lacrimation, nasal congestion, miosis, or ptosis.	- **Acute**: **Sumatriptan (subcutaneous)**: 6 mg, max 12 mg/day. **Oxygen**: 12-15 L/min for 15-20 minutes. - **Prophylaxis**: **Verapamil**: 240-960 mg/day, titrated based on response.
Medication Overuse Headache	- Headache ≥15 days/month due to medication use for >3 months.	- **Management**: Withdraw overused medication abruptly for simple analgesics and triptans. - **Bridge Therapy** (if needed): **Naproxen**: 250-500 mg twice daily. **Prednisone**: 20-40 mg/day, tapered over 1-2 weeks.
Idiopathic Intracranial Hypertension (IIH)	- Chronic headache with postural component, papilloedema, normal imaging, and elevated CSF pressure.	- **Initial Treatment**: **Acetazolamide**: 250-500 mg twice daily, max 1,000 mg/day. - **Alternative**: **Topiramate**: 25-100 mg/day. - **Surgical Options**: LP shunt for severe cases.

Migraine
- acute: triptan + NSAID or triptan + paracetamol
- prophylaxis: topiramate or propranolol

Distinguishing cluster headaches and Chronic Paroxysmal Hemicrania

Cluster headache	Chronic Paroxysmal Hemicrania
more common in males	more common in females
frequency of attacks is 1 - 4 (maximum 8) in 24 hours.	the **frequency** of attacks is **higher**, usually more than 15 in 24 hours
The duration of headaches is (15-60 min).	The **duration** of headaches is **shorter** (2-25 min)
Not responds to indomethacin	**responds very well to indomethacin**

Cluster headache - acute treatment: subcutaneous sumatriptan + 100% O2

Cluster headaches may involve pain around one eye, along with drooping of the lid, tearing and congestion on the same side as the pain

Triptans

Action

- Triptans are specific **5-HT1 agonists** used in the acute treatment of migraine.
- They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points

- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

- 'triptan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications

- patients with a history of, or significant risk factors for, ischaemic heart disease or cerebrovascular disease

Epilepsy is not a contraindication to the use of triptans

Idiopathic intracranial hypertension(IIH)

Obese, young female with headaches / blurred vision : think idiopathic intracranial hypertension

Postural headache but normal imaging → idiopathic intracranial hypertension

Suspected Idiopathic intracranial hypertension → lumbar puncture to confirm the diagnosis is the next step

Overview

- also known as pseudotumour cerebri and formerly benign intracranial hypertension
- classically seen in young, overweight females.

Risk factors

- obesity
- female sex
- pregnancy
- drugs:
  - ⇨ **oral contraceptive pill (eg: Dianette),**
  - ⇨ Danazol (synthetic androgen used to treat endometriosis)
  - ⇨ **steroids**,
  - ⇨ **tetracycline**,
  - ⇨ **vitamin A**,
  - ⇨ Nalidixic acid
  - ⇨ *if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

Features

- headache
  - ⇨ chronic postural headache (suggested by its improvement as the day progresses)
  - ⇨ 10% of cases are free of headaches.
- blurred vision, (Horizontal diplopia)
  - ⇨ Diplopia is common due to sixth nerve palsy.
- papilloedema (usually present)
- **enlarged blind spot**
- Reduction in colour vision is common
- sixth nerve palsy may be present
- normal appearances of the magnetic resonance imaging (MRI). Normal ventricular size, anatomy and position. Normal CSF cell count and protein content.
- **plantars are flexor**
  - ⇨ Extensor plantars suggest alternative diagnosis.
- **Absence of retinal venous pulsations**

Diagnosis

- the diagnosis is confirmed by finding an **elevated CSF opening pressure** (more than 20 cm H_2O). CSF protein, glucose and cell count will be normal.
- CT and MRI scans are often normal
  - ⇨ CT brain is needed to exclude a space occupying lesion and obstructing hydrocephalus.
  - ⇨ **MRI venogram is recommended afterwards to exclude cerebral sinus thrombosis.**

Management

- weight loss
- diuretics e.g. acetazolamide
- topiramate (anticonvulsant) is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery:
  - ⇨ A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure
  - ⇨ optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve.
    - **In progressive visual loss → Lumbo-peritoneal (LP) shunt is the treatment of choice.**
      - ❖ Optic nerve fenestration is an alternative.
      - ❖ There are no comparative studies between the two interventions.

Complication

- Progressive visual loss and optic atrophy

Multiple sclerosis (MS)

Definition

- A chronic, immune-mediated disorder characterized by inflammation, demyelination, and axonal degeneration in the central nervous system (CNS).

Epidemiology

- More common in women (2-3:1 ratio).
- Typical age of onset: 20-40 years.
- Higher prevalence in temperate regions (e.g., Northern Europe, North America).

Pathophysiology

- The immune system mistakenly attacks the myelin sheath, leading to disrupted nerve signal transmission.
- Areas of demyelination (plaques) form in the CNS, most commonly affecting the optic nerves, spinal cord, brainstem, and cerebellum.

Types of MS

- **Relapsing-Remitting MS (RRMS)**: Most common form; periods of exacerbations followed by remissions.
- **Secondary Progressive MS (SPMS)**: Progresses from RRMS with continuous neurological decline.

- **Primary Progressive MS (PPMS)**: Steady progression of symptoms without relapses from the onset.
- **Progressive-Relapsing MS (PRMS)**: Rare; progressive disease with occasional acute relapses.

Clinical Features

- **Common Initial Symptoms**:
  - Visual disturbances (e.g., optic neuritis: pain and vision loss in one eye).
  - Sensory changes (e.g., paresthesia, numbness).
  - Weakness or motor dysfunction.
  - Coordination problems and ataxia.
- **Other Symptoms**:
  - Fatigue, spasticity, bladder and bowel dysfunction, cognitive impairment, depression.
  - Lhermitte's sign: Electric shock-like sensation down the spine when flexing the neck.
  - Uhthoff's phenomenon: Symptom worsening with heat exposure.

Diagnosis

- **Clinical Criteria**: Based on episodes of neurological symptoms separated in time and space.
- **MRI**: Demonstrates white matter lesions in the brain and spinal cord.
- **CSF Analysis**:
  - Presence of **oligoclonal bands** and increased **IgG index**.
- **Evoked Potentials**: Visual or somatosensory evoked potentials can reveal slowed nerve conduction.

Management

- **Acute Relapse**:
  - **Corticosteroids** (e.g., IV methylprednisolone 500-1,000 mg/day for 3-5 days).
- **Disease-Modifying Therapies (DMTs)**:
  - **First-Line**: Interferon-beta, glatiramer acetate.
  - **Oral Options**: Dimethyl fumarate, teriflunomide.
  - **Second-Line**: Natalizumab, ocrelizumab, fingolimod.
- **Symptomatic Treatment**:
  - **Spasticity**: Baclofen or tizanidine.
  - **Fatigue**: Amantadine or modafinil.
  - **Pain**: Gabapentin or pregabalin for neuropathic pain.
- **Physical and Occupational Therapy**: To improve functional outcomes and manage disability.

Prognosis

- Variable and depends on disease subtype and response to treatment.
- Many patients with RRMS transition to SPMS over time.
- PPMS generally has a worse prognosis with continuous progression.

Diagnostic Criteria for MS (Revised McDonald Criteria 2017)

Criteria	Description
Dissemination in Time (DIT)	- **Met**: ≥ 2 exacerbations occurring at least 30 days apart. - **Not Met**: Confirm by one of the following: • Additional exacerbation. • MRI showing both gadolinium-enhancing and non-enhancing lesions at any time, or a new T2 or enhancing lesion on follow-up MRI. • Presence of **oligoclonal bands** in CSF.
Dissemination in Space (DIS)	- **Met**: ≥ 2 lesions with objective clinical evidence in MS-typical regions (periventricular, juxtacortical, infratentorial, or spinal cord). - **Not Met**: Confirm by one of the following: • Additional exacerbation involving a different CNS region. • MRI showing ≥ 1 T2-hyperintense lesion in at least 2 of the following regions: periventricular, juxtacortical, infratentorial, or spinal cord.
Next Investigation if Brain MRI is Inconclusive	**MRI Spinal Cord**: More specific for inflammatory disorders like MS; useful to distinguish from ischaemic lesions.

Management of MS Summary Table

Treatment Category	Details with Drug Doses and Notes
Acute Exacerbations	- **First-line**: **Methylprednisolone** **Oral**: 0.5 g/day for 5 days (outpatient). **IV**: 1 g/day for 3-5 days (if hospitalised or oral steroids fail).
Second-line for Relapses	**Plasmapheresis**: Used if steroids are ineffective or contraindicated.
Disease-Modifying Therapy (DMT)	- **First-line**: **Beta-interferon** and **Glatiramer acetate** **Beta-interferon**: Reduces relapse rate by ~30%; not indicated if ≥3 relapses/year. **Glatiramer acetate**: Safe in pregnancy; may cause chest pain and lipoatrophy.
Monoclonal Antibodies	- **Natalizumab**: Monthly IV infusions; monitor for PML risk, test for anti-JCV antibodies every 6 months. - **Ocrelizumab/Ofatumumab**: Anti-CD20 monoclonal antibodies that deplete B cells; used for early primary progressive MS.
Oral Therapies	- **Cladribine**: For highly active MS with specific MRI criteria. - **Teriflunomide**: Once daily; may cause GI symptoms and elevated liver enzymes. - **Fingolimod/Ponesimod**: S1P receptor modulators; used when first-line therapies fail. **Note**: Monitor for varicella zoster and progressive multifocal leukoencephalopathy (PML).

Symptomatic Treatments for MS Summary Table

Symptom	Treatment with Drug Doses and Notes
MS-Related Fatigue	- **Non-pharmacological**: Exercise, Cognitive Behavioral Therapy (CBT). - **Pharmacological**: **Amantadine**: 100 mg twice daily. **Modafinil**: 100-200 mg once or twice daily (avoid in pregnancy).
Spasticity	- **First-line**: **Baclofen** (5-10 mg three times daily, max 80 mg/day). - **Second-line**: **Gabapentin** (start at 300 mg once daily, titrate to 900-2,400 mg/day in divided doses). - **Combination Therapy**: Baclofen and gabapentin if single therapy is inadequate.
Oscillopsia	- **First-line**: **Gabapentin** (start at 300 mg once daily, titrate as needed). - **Second-line**: **Memantine** (5-20 mg daily, titrated gradually).
Emotional Lability	- **Amitriptyline**: 10-25 mg at night, titrate as needed.
Neuropathic Pain	- **First-line**: **Amitriptyline** (10-25 mg at night, increase as needed), **Duloxetine** (30-60 mg daily), **Gabapentin** (900-2,400 mg/day in divided doses), **Pregabalin** (75-150 mg twice daily). - **Second-line**: Switch to another first-line drug.
Bladder Dysfunction	- **Initial Assessment**: Ultrasound to evaluate bladder emptying. - **Significant Residual Volume**: Intermittent catheterisation. - **No Significant Residual Volume**: **Anticholinergics** (e.g., oxybutynin: 2.5-5 mg three times daily).

Baclofen

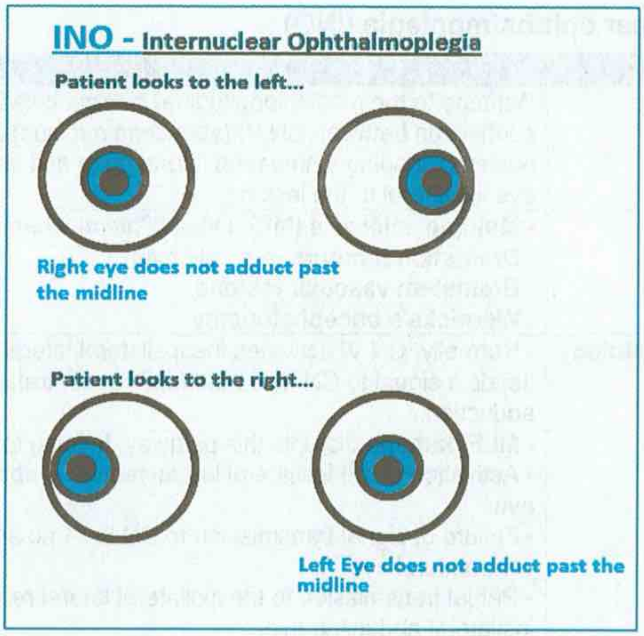
Aspect	Details
Action	**Gamma-aminobutyric acid-B (GABA) receptor agonist → Skeletal muscle relaxant**
Indications	- Hiccups - Muscle spasm and musculoskeletal pain - Spasticity
Doses	- **Usual Dose**: 5 mg 3 times daily; increase by 5 mg per dose every 3 days. - **Maximum Dose**: 80 mg per day (20 mg 4 times per day). - **Renal Dosing**: • CrCl <30 mL/min: avoid use. • CrCl 30 to <50 mL/min: reduce by 50% (2.5 mg every 8 hours). • CrCl 50 to 80 mL/min: 5 mg every 12 hours. - **Hepatic Dosing**: No adjustments needed.
Discontinuation	Discontinue slowly over 1-2 weeks to prevent withdrawal symptoms (e.g., nausea, vomiting, weakness, confusion, dizziness, hallucinations, seizures).
Side Effects	Drowsiness, dizziness, weakness, fatigue

Internuclear ophthalmoplegia (INO)

Aspect	Details
Definition	Damage to the medial longitudinal fasciculus (MLF) disrupting the connection between CN VI (abducens nucleus) and CN III (oculomotor nucleus), leading to impaired lateral gaze and impaired adduction of the eye ipsilateral to the lesion.
Causes	- **Multiple sclerosis (MS)**: Often bilateral, characteristic of MS. - **Brainstem tumours** (e.g., gliomas). - **Brainstem vascular lesions**. - **Wernicke's encephalopathy**.
Pathophysiology	- Normally, CN VI activates the ipsilateral lateral rectus for abduction and sends a signal to CN III via the MLF for contralateral medial rectus adduction. - **MLF damage** disrupts this pathway, leading to: • Activation of the ipsilateral lateral rectus → abduction of the ipsilateral eye. • Failure of signal transmission to CN III → no adduction of the contralateral eye. • Partial transmission to the ipsilateral lateral rectus → nystagmus of the ipsilateral abducting eye.
Clinical Findings	- **Limited adduction** during horizontal eye movements. - **Retained adduction** during convergence. - **Horizontal diplopia**. - **Dissociated nystagmus**: Nystagmus in the contralateral eye when gazing to the opposite side.

Internuclear ophthalmoplegia (INO)

- **Ipsilateral abduction impairment and Nystagmus on the Opposite side.**
- **When covering one eye, unilateral movements will be normal. But when together, the adducting eye will not move past the midline.**



Myasthenia gravis (MG)

Definition:

- Myasthenia Gravis is an autoimmune neuromuscular disorder characterized by fluctuating muscle weakness and fatigability due to autoantibodies targeting acetylcholine receptors (AChR) or other neuromuscular junction components.

Pathophysiology:

- Autoantibodies block or destroy AChRs, impairing neuromuscular transmission and leading to muscle weakness.

Clinical Features:

- **Muscle Weakness**: Typically worsens with activity and improves with rest.
- **Commonly Affected Muscles**:
  - **Ocular**: Ptosis, diplopia.
  - **Bulbar**: Dysarthria, dysphagia.
  - **Limb**: Proximal muscle weakness.
- **Myasthenic Crisis**: Severe respiratory muscle involvement that requires emergency treatment.

Diagnosis:

- **Clinical Assessment**: Observation of fatigability and muscle weakness.
- **Edrophonium (Tensilon) Test**: Transient improvement of muscle strength following administration.
- **Antibody Testing**: Detection of anti-AChR or anti-MuSK antibodies.
- **Electrophysiological Tests**: Repetitive nerve stimulation and single-fiber EMG showing decreased response.

Management:

- **First-Line Treatment**:

- Acetylcholinesterase Inhibitors:
  - **Pyridostigmine**: Initial dose of 30-60 mg orally 3-4 times daily, with a possible increase up to 120 mg every 3-4 hours based on clinical response.
- **Immunosuppressive Therapy**:
  - **Corticosteroids**:
    - **Prednisone**: Start at 5-10 mg/day, gradually increasing to 1 mg/kg/day as needed.
  - **Steroid-Sparing Agents**:
    - **Azathioprine**: 2-3 mg/kg/day.
    - **Mycophenolate Mofetil**: 1-1.5 g twice daily.
- **Advanced Treatments**:
  - **IV Immunoglobulin (IVIG)**: Used for acute exacerbations; administered as 2 g/kg divided over 2-5 days.
  - **Plasmapheresis**: Employed during myasthenic crises or severe relapses.
- **Surgical Treatment**:
  - **Thymectomy**: Indicated for patients with thymoma and can be beneficial for those with generalized MG to improve long-term outcomes.

Side Effects of Key Medications:

- **Pyridostigmine**: Gastrointestinal upset, muscle cramps, sweating.
- **Corticosteroids**: Long-term use can lead to weight gain, osteoporosis, and hyperglycemia.
- **Azathioprine**: Risk of bone marrow suppression and hepatotoxicity.

Myasthenic crisis VS Cholinergic crisis

Aspect	Myasthenic Crisis	Cholinergic Crisis
Definition	Acute, life-threatening exacerbation of myasthenic symptoms leading to respiratory failure.	Excessive cholinergic stimulation due to overuse of acetylcholinesterase inhibitors, mimicking organophosphate poisoning.
Cause	Triggers include infections, surgery, anesthesia, pregnancy, and certain medications.	Overuse of pyridostigmine or other acetylcholinesterase inhibitors.
Pathophysiology	Insufficient acetylcholine at the neuromuscular junction leading to severe muscle weakness.	Excess acetylcholine at the neuromuscular junction leading to overstimulation and muscle fatigue.
Clinical Features	- Severe muscle weakness. - Respiratory distress (reduced breath count, chest expansion, oxygen saturation).	- Bradycardia, hypotension, bronchospasm. - Abdominal cramps, diarrhea. - Flaccid paralysis of the extremities.
Diagnosis	- **Edrophonium (Tensilon) Test**: Temporary improvement of symptoms.	- **Edrophonium Test**: No improvement or worsening of symptoms.
Management	- **IV Immunoglobulins (IVIg)**: 400 mg/kg for 5 days. - **Plasmapheresis**: Rapid effect. - **Early intubation** if vital capacity < 20 mL/kg.	- **Atropine**: To counteract cholinergic effects. - Discontinue or reduce acetylcholinesterase inhibitors.

Lambert-Eaton myasthenic syndrome (LEMS)

Definition

- Rare autoimmune disease that reduces neuromuscular transmission, leading to muscle weakness

Prevalence

- Occurs in males more often than females (5:1).

Aetiology

- Paraneoplastic: associated with small-cell lung carcinoma (in ⅔ of LEMS cases)
- May also occur independently as an autoimmune disorder.

Pathophysiology

- **Autoantibodies directed against presynaptic voltage-gated calcium channels** (anti-VGCC antibodies) → ↓ Ca^{2+} influx → ↓ presynaptic vesicle fusion → impaired acetylcholine release in the neuromuscular junction (NMJ)

Features

- Proximal muscle weakness
- **Repeated muscle contractions lead to increased muscle strength** (in contrast to myasthenia gravis)
- **Reduced or absent reflexes** (in contrast to myasthenia gravis where the reflexes are normal or brisk)
- **Autonomic symptoms:** dry mouth, impotence, difficultly micturating.
- Ophthalmoplegia and ptosis are not common (unlike in myasthenia gravis)

Diagnostics

- Active muscle contraction or repeated muscle tapping increases reflex activity.
- Lambert sign: **a patient's muscle strength improves with repetitive or ongoing use**
- **EMG: Repetitive nerve stimulation results in incremental responses.**
- **Confirmatory test:** serologic detection of anti-VGCC antibodies

Treatment

- First-line to improve neuromuscular transmission: amifampridine

Myasthenia gravis VS Lambert-Eaton

	Myasthenia gravis	Lambert-Eaton
Muscle weakness	Proximal muscle weakness: face, neck, limb girdle	Affects lower limbs first
Muscle power following exercise	Becomes weaker	Temporary increase
Reflexes	Normal or brisk	Absence or hyporeflexia
Autonomic dysfunction	None	Common
Antibodies	Antibodies to acetylcholine receptors	Antibody directed against pre-synaptic voltage gated calcium channel
Commonly associated tumor	Thymomas or thymic hyperplasia	Small cell lung cancer

Neurofibromatosis (NF)

Definition

- **Neurofibromatosis** is a genetic disorder characterized by the development of multiple nerve sheath tumors and various other systemic manifestations. There are two main types:
  - **NF type 1 (NF1)**, also known as *von Recklinghausen disease*.
  - **NF type 2 (NF2)**, associated with bilateral vestibular schwannomas.

Comparison of Neurofibromatosis Type 1 (NF1) and Neurofibromatosis Type 2 (NF2)

Feature	NF1	NF2
Genetics	Mutation in **NF1 gene** on chromosome **17**	Mutation in **NF2 gene** on chromosome **22**
Protein Involved	**Neurofibromin** (tumor suppressor)	**Merlin (schwannomin)** (tumor suppressor)
Incidence	More common (1 in 3,000 individuals)	Less common (1 in 25,000 individuals)
Inheritance Pattern	Autosomal dominant	Autosomal dominant
Hallmark Tumors	**Neurofibromas** (skin and deeper tissue)	**Bilateral vestibular schwannomas**
Skin Manifestations	**Café-au-lait spots, axillary/inguinal freckling**	Skin schwannomas (less common than NF1)
Ophthalmologic Findings	**Lisch nodules** (iris hamartomas)	**Early-onset cataracts**
CNS Tumors	**Optic gliomas**	**Meningiomas, ependymomas,** and **schwannomas**
Neurological Features	**Learning disabilities, seizures**	**Hearing loss, balance issues, tinnitus**
Key Complications	**Malignant peripheral nerve sheath tumors (MPNST)**	**Complete hearing loss**, neurological deficits
Diagnostic Criteria	Requires 2 or more characteristic features (e.g., café-au-lait spots, neurofibromas, etc.)	Bilateral vestibular schwannomas or specific family history
Management Approach	Symptom monitoring, surgery for neurofibromas if needed, treat complications (e.g., hypertension)	Hearing rehabilitation, tumor removal, use of **bevacizumab** to shrink schwannomas
Prognosis	Generally good but varies based on tumor burden and complications	Dependent on tumor burden; risk of significant hearing loss

Summary

- **NF1** primarily affects the **skin and peripheral nervous system**, leading to cutaneous manifestations, learning disabilities, and optic pathway gliomas.
- **NF2** predominantly involves the **central nervous system**, with bilateral vestibular schwannomas as the defining feature, along with other CNS tumors and associated hearing loss.

Tuberous sclerosis (TS)

Definition

- **Tuberous sclerosis (TS)** is a rare, multisystem genetic disorder characterized by the development of benign tumors in various organs, primarily the brain, skin, kidneys, heart, lungs, and eyes.

Pathophysiology

- Caused by mutations in either the **TSC1 gene** (chromosome 9) encoding **hamartin** or the **TSC2 gene** (chromosome 16) encoding **tuberin**.
- These proteins form a complex that inhibits the **mTOR (mammalian target of rapamycin)** pathway, which regulates cell growth and proliferation. Mutations lead to unregulated cell growth and the formation of hamartomas.

Clinical Features

- **Neurological**:
  - **Seizures**: Common and often the first sign in infancy (e.g., infantile spasms).
  - **Cognitive impairment**: Intellectual disability or developmental delay.
  - **Behavioral disorders**: Autism spectrum disorder, hyperactivity, and aggressive behaviors.
- **Dermatological**:
  - **Hypomelanotic macules (ash-leaf spots)**: White, depigmented skin patches.
  - **Facial angiofibromas**: Red papules, often on the face (cheeks and nose).
  - **Shagreen patches**: Thick, leathery skin typically on the lower back.
  - **Periungual fibromas**: Tumors around the nail beds.
- **Renal**:
  - **Angiomyolipomas**: Benign tumors composed of blood vessels, muscle, and fat.
  - **Cysts**: Can lead to chronic kidney disease.
- **Cardiac**:
  - **Rhabdomyomas**: Cardiac tumors that can be detected prenatally or in infancy.
- **Pulmonary**:
  - **Lymphangioleiomyomatosis (LAM)**: Primarily affects women and can lead to progressive lung disease.
- **Ophthalmologic**:
  - **Retinal hamartomas**.

Complications

- **Neurological**:
  - **Seizures** may become refractory, leading to **epileptic encephalopathy**.
  - **Subependymal giant cell astrocytomas (SEGA)**: Can cause hydrocephalus due to obstruction.
- **Renal**:
  - Risk of **renal failure** due to angiomyolipomas or cysts.
- **Pulmonary**:
  - **LAM** can lead to respiratory failure.
- **Cardiac**:
  - Cardiac tumors (rhabdomyomas) may interfere with cardiac function but often regress spontaneously.

Diagnostic Criteria

- **Definite TS**: Presence of **two major** or **one major and ≥2 minor** features.
- **Major criteria**:
  - Cortical tubers
  - Subependymal nodules
  - Hypomelanotic macules (≥3, at least 5mm diameter)
  - Facial angiofibromas or fibrous cephalic plaque
  - Shagreen patch
  - Cardiac rhabdomyoma
  - Lymphangioleiomyomatosis (LAM)
  - Angiomyolipomas (≥2)
- **Minor criteria**:
  - Dental enamel pits (≥3)
  - Hamartomatous rectal polyps
  - Bone cysts
  - Cerebral white matter migration lines
  - Retinal achromic patch
  - Confetti skin lesions

Treatment

- **Seizure management**:
  - **Antiepileptic drugs (AEDs)** for seizure control.
  - **Vagus nerve stimulation (VNS)** or **surgical resection** for refractory cases.
- **mTOR inhibitors**:
  - **Everolimus**: Effective for shrinking SEGAs and renal angiomyolipomas (side effects: mouth ulcers, infections).
- **Behavioral therapy**:
  - Addressing cognitive and behavioral challenges with tailored therapies.
- **Surgical intervention**:
  - For symptomatic SEGAs or large angiomyolipomas.
- **Monitoring**:
  - Regular follow-ups with **MRI** for brain lesions, **renal ultrasound/CT**, and **pulmonary function tests**.

Laboratory and Imaging Findings

- **Brain MRI**: Identifies cortical tubers, subependymal nodules, and SEGAs.
- **Ultrasound/CT of kidneys**: Detects angiomyolipomas and cysts.
- **Echocardiogram**: Evaluates cardiac rhabdomyomas.
- **Pulmonary function tests** and **high-resolution CT (HRCT)**: Assess for LAM in adults, especially females.

Key Points

- **TSC1 and TSC2 gene mutations** are pivotal in diagnosis.
- **Seizures** and **cognitive impairments** are early and prominent features.
- **Hypomelanotic macules** and **facial angiofibromas** are dermatological hallmarks.
- **mTOR inhibitors** (e.g., **everolimus**) are critical for the treatment of certain TS manifestations.

Brain Tumors

Tumor Type	Origin	Common Location	Key Features	Imaging Findings
Glioblastoma Multiforme (GBM)	Glial cells (astrocytes)	Cerebral hemisphere	Highly aggressive, rapid progression, headaches, seizures, focal neurological deficits	MRI: Irregular, ring-enhancing mass with central necrosis, surrounding edema
Meningioma	Meningothelial cells	Extra-axial, near dural surfaces	Often benign, slow-growing, may cause compression symptoms	MRI/CT: Homogeneous, well-circumscribed mass, dural attachment ("dural tail")
Medulloblastoma	Embryonal cells	Posterior fossa (cerebellum)	Common in children, ataxia, signs of increased intracranial pressure	MRI: Midline mass, often with hydrocephalus
Ependymoma	Ependymal cells	Fourth ventricle (children), spinal cord (adults)	Obstructive hydrocephalus, focal neurological signs	MRI: Well-circumscribed, enhancing intraventricular mass
Oligodendroglioma	Oligodendrocytes	Frontal and temporal lobes	Seizures, slow progression, calcifications common	MRI/CT: Calcified mass, "fried egg" appearance on histology
Pituitary Adenoma	Pituitary gland cells	Sella turcica	Hormonal imbalances (e.g., prolactinoma, acromegaly), visual disturbances due to optic chiasm compression	MRI: Sellar mass with possible suprasellar extension
Schwannoma	Schwann cells	Cerebellopontine angle (CN VIII)	Hearing loss, tinnitus, balance problems	MRI: Well-defined, enhancing mass at the internal auditory canal

Tumor Type	Origin	Common Location	Key Features	Imaging Findings
Craniopharyngioma	Rathke's pouch remnants	Suprasellar region	Bitemporal hemianopia, endocrine dysfunction	MRI/CT: Cystic/solid mass with calcifications
Astrocytoma (Grade I-IV)	Astrocytes	Anywhere in CNS	Grades I (pilocytic) to IV (GBM), progressive symptoms	MRI: Low to high-grade features, enhancing/non-enhancing depending on grade
Primary CNS Lymphoma	Lymphoid cells	Periventricular white matter	Cognitive changes, focal deficits, immunocompromised patients at higher risk	MRI: Homogeneously enhancing lesions, often crossing the midline

Von Hippel-Lindau syndrome (VHL)

Definition

- **Von Hippel-Lindau (VHL) syndrome** is an autosomal dominant genetic disorder characterized by the development of benign and malignant tumors in multiple organ systems.

Pathophysiology

- Caused by mutations in the **VHL gene** on chromosome **3p25-26**.
- The **VHL protein** regulates cellular responses to hypoxia. Mutations result in dysregulated cell growth and tumor development.

Clinical Features

- **CNS and Retinal Hemangioblastomas**:
  - Commonly found in the cerebellum, spinal cord, and retina.
  - Can cause headaches, ataxia, or visual disturbances depending on location.
- **Renal Cell Carcinoma (RCC)**:
  - Clear cell type, often bilateral and multifocal.
- **Pheochromocytomas**:
  - May present with hypertension, palpitations, and headaches.
- **Pancreatic Cysts and Neuroendocrine Tumors**:
  - Cysts are usually asymptomatic, while neuroendocrine tumors can produce hormonal symptoms.
- **Endolymphatic Sac Tumors**:
  - Can lead to hearing loss and balance issues.
- **Epididymal and Broad Ligament Cysts**:
  - Non-cancerous but characteristic of VHL.

Complications

- **Cerebellar Hemangioblastomas**: Can lead to hydrocephalus and increased intracranial pressure.
- **Renal Cell Carcinoma**: High risk of metastasis if not detected early.
- **Pheochromocytomas**: Can cause life-threatening hypertensive crises.

Diagnostic Criteria

- **Clinical diagnosis**: Based on family history and characteristic tumor types.
- **Genetic testing**: Confirmation by identifying **VHL gene mutations**.
- **Imaging**: MRI of the brain and spine, abdominal CT/MRI, and ophthalmologic evaluation.

Management

- **Surveillance**:
  - Regular screening for early detection of tumors (e.g., annual MRI of the CNS, abdominal imaging, and retinal exams).
- **Surgical treatment**:
  - **Hemangioblastomas**: Surgical resection if symptomatic.
  - **Renal tumors**: Partial nephrectomy to preserve renal function.
- **Medical management**:
  - **Pheochromocytomas**: Managed with alpha-blockers followed by beta-blockers prior to surgical removal.
- **mTOR inhibitors**: May be used in certain cases to manage tumors (e.g., RCC).

Key Points

- **Autosomal dominant inheritance** with **high penetrance**.
- Early detection and regular **multisystem screening** are essential for patient outcomes.
- **CNS hemangioblastomas** and **RCC** are the most significant contributors to morbidity and mortality.
- **Genetic counseling** is crucial for affected families.
- **Pheochromocytomas** associated with VHL are often **non-malignant** but can be life-threatening if undiagnosed.

Early age SAH occur in Von Hippel Lindau

Wernicke's encephalopathy

Definition

- Wernicke's encephalopathy is a neuropsychiatric disorder caused by **thiamine deficiency**, which is most commonly seen in alcoholics.

Causes

- **Most common: alcohol**
- **Rarer causes include**:
  - ⇨ persistent vomiting,
  - ⇨ stomach cancer,
  - ⇨ dietary deficiency.

Features

- nystagmus (the most common ocular sign)
- ophthalmoplegia

- ataxia
- confusion, altered GCS
- peripheral sensory neuropathy
- Sometimes bilateral wrist drop but more frequently bilateral foot drop with pain or pressure over the long nerves.
- petechial haemorrhages occur in a variety of structures in the brain including the mamillary bodies and ventricle walls

Investigations

- **1st investigations to order → therapeutic trial of parenteral thiamine**
- decreased red cell transketolase
- MRI

Treatment is with urgent replacement of **thiamine (Pabrinex (Intravenous))**

> **Wernicke's encephalopathy: classic triad of:**
> 1. **nystagmus,**
> 2. **ophthalmoplegia**
> 3. **ataxia**

Korsakoff syndrome

> **Korsakoff's syndrome: Inability to acquire new memories and confabulation**

Definition

- a late neuropsychiatric manifestation of Wernicke encephalopathy.

Pathophysiology

- alcohol → vitamin B1 (thiamine) deficiency → damage to mammillary bodies (structures of the limbic system)

Feature

- Wernicke's encephalopathy + antero- and retrograde **amnesia** and **confabulation**.
  - ⇨ confabulation (false memories) is a disturbance of memory, defined as the production of fabricated memories without the conscious intention to deceive.
  - ⇨ dementia is typically not reversible.

Investigations

- MRI finding → **mammillary body degeneration**

Treatment

- maintenance thiamine and rehabilitation

Anti-NMDA receptor encephalitis (Autoimmune encephalitis)

Definition

- It is a type of brain inflammation due to antibodies. (a paraneoplastic syndrome), presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability.
- might be misdiagnosed as a primary psychiatric illness.

Mechanism

- **autoimmune** with the primary target the N-methyl D-aspartate receptors (NMDAR) in the brain

Epidemiology

- 80% are female
- particularly prevalent in Afro-Caribbean patients.

Associations

- Ovarian teratomas are detected in up to half of all female adult patients,

Investigations

- CSF
  - ⇨ can be normal initially.
  - ⇨ may demonstrate pleocytosis
  - ⇨ **antibodies against NMDA receptors**
  - ⇨ CSF titers of anti-NMDA receptor antibodies correlate with clinical illness
- MRI head
  - ⇨ can be normal in 50%
  - ⇨ abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures.
- evaluation for an ovarian teratoma by MRI, CT scan, or ultrasound

Treatment

- immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination.
- Resection of teratoma is also therapeutic.

Spinal cord and peripheral nerve lesions

Lower back pain

Definition

- **Lower back pain (LBP)** refers to pain located between the lower rib margins and the buttock creases. It can be classified as **acute** (lasting less than 6 weeks), **subacute** (6–12 weeks), or **chronic** (lasting more than 12 weeks).

Classification

- **Non-specific LBP**: No identifiable specific pathology (most common).
- **Specific LBP**: Associated with identifiable conditions, such as:
  - **Herniated disc**
  - **Spinal stenosis**
  - **Vertebral fractures**
  - **Infections (e.g., osteomyelitis)**
  - **Malignancies (e.g., metastasis)**
  - **Inflammatory conditions (e.g., ankylosing spondylitis)**

Pathophysiology

- May involve a combination of **muscle strain**, **ligament sprain**, **degenerative disc disease**, or **facet joint dysfunction**.
- Chronic LBP may result from persistent nociceptive pain or sensitization leading to chronic pain syndromes.

Clinical Features

- **Non-specific LBP**:
  - Dull, aching pain localized to the lower back.
  - May radiate to the buttocks or thighs but not beyond the knee.
  - Pain often worsens with movement and improves with rest.
- **Red flag symptoms** (suggesting serious underlying conditions):
  - **Unexplained weight loss**
  - **History of cancer**
  - **Fever or recent infection**
  - **Neurological deficits** (e.g., weakness, numbness)
  - **Saddle anesthesia or bowel/bladder dysfunction** (suggestive of cauda equina syndrome)

Diagnosis

- **Clinical assessment**:
  - **History** and **physical examination** to rule out red flags.
  - **Neurological examination** to assess for radiculopathy or other deficits.
- **Imaging** (not routinely indicated for non-specific LBP):
  - **MRI**: Preferred for suspected neurological involvement or red flag symptoms.
  - **X-ray**: For suspected fractures or significant structural issues.
- **Laboratory tests**:
  - Only if infection or systemic disease is suspected (e.g., CRP, ESR, CBC).

Management

- **Non-specific LBP**:
  - **Education and reassurance**: Explain the benign nature of most cases.
  - **Physical activity**: Encourage continued activity and normal daily functions.
  - **First-line treatment**:
    - **Analgesics**: Paracetamol or NSAIDs.
    - **Topical treatments**: NSAIDs or capsaicin.
  - **Second-line treatment**:
    - **Muscle relaxants** or **opioids** (short-term use only).
- **Chronic LBP**:
  - **Multimodal approach**:
    - **Physical therapy**: Core strengthening and stretching exercises.
    - **Cognitive-behavioral therapy (CBT)**.
    - **Pharmacological**: Tricyclic antidepressants or duloxetine for neuropathic pain.
- **Specific LBP**:
  - **Herniated disc**: May require surgical intervention (e.g., discectomy) if neurological deficits persist.
  - **Spinal stenosis**: Conservative treatment first; surgery if significant functional impairment.
  - **Infections and malignancies**: Require targeted treatment (e.g., antibiotics, chemotherapy, or surgery).

Transverse Myelitis (TM)

Definition

- **Transverse myelitis (TM)** is an inflammatory disorder of the spinal cord characterized by acute or subacute motor, sensory, and autonomic dysfunction.

Etiology

- **Idiopathic**: No known cause.
- **Autoimmune**:
  - Associated with diseases like **multiple sclerosis (MS)** and **neuromyelitis optica (NMO)**.
- **Post-infectious**:
  - Viral (e.g., herpes simplex, varicella-zoster, enteroviruses).
  - Bacterial (e.g., Lyme disease, Mycoplasma pneumoniae).
- **Paraneoplastic**: Associated with underlying malignancies.
- **Systemic inflammatory conditions**:
  - **Lupus**, **sarcoidosis**, **Sjogren's syndrome**.

Pathophysiology

- Inflammation leads to demyelination and neuronal damage, disrupting the normal function of the spinal cord. This can affect specific tracts, resulting in various neurological deficits.

Clinical Features

- **Motor Symptoms**:
  - Weakness that may progress from paresis to paralysis, often with an ascending pattern.

- **Sensory Symptoms**:
  - Sensory loss or paraesthesia (e.g., numbness, tingling).
  - Level-specific sensory changes (typically with a defined spinal level).
- **Autonomic Dysfunction**:
  - Bladder and bowel dysfunction.
  - Sexual dysfunction.
- **Pain**:
  - Often severe back or radicular pain at the onset.
- **Bilateral Presentation**:
  - Although symptoms can be asymmetric, they are commonly bilateral.

Diagnosis

- **Clinical evaluation**:
  - History and physical examination to assess the level of neurological involvement.
- **MRI**:
  - T2 hyperintensity within one or more contiguous vertebral segments.
  - Possible enhancement with gadolinium.
- **Lumbar puncture**:
  - May show elevated protein and pleocytosis, suggestive of inflammation.
  - Oligoclonal bands may indicate an association with **MS**.
- **Blood tests**:
  - Rule out infectious or autoimmune causes (e.g., NMO antibodies, ANA, specific viral serologies).

Treatment

- **First-line therapy**:
  - **High-dose corticosteroids** (e.g., IV methylprednisolone for 3-5 days).
- **Second-line therapy**:
  - **Plasma exchange (PLEX)** if there is inadequate response to corticosteroids.
- **Targeted therapy**:
  - For TM associated with specific conditions (e.g., **immunosuppressive therapy** for autoimmune conditions like NMO).
- **Supportive management**:
  - **Physical and occupational therapy** to aid recovery and improve function.
  - **Pain management**: Analgesics, neuropathic pain agents (e.g., gabapentin, pregabalin).

Metastatic spinal cord compression

Epidemiology

- Affects up to **5% of cancer patients**, considered an **oncological emergency**.

Causes

- Primarily due to **extradural compression** from vertebral body metastases.
- Commonly seen in **lung, breast, and prostate cancer** patients.

Symptoms

- **Back pain**:
  - Earliest and most common symptom.
  - Worsens when lying down or coughing.
- **Neurological signs**:
  - **Lower limb weakness** and sensory changes (e.g., numbness).

- Signs vary with lesion level:
  - **Above L1**: Upper motor neuron signs in legs, sensory level present.
  - **Below L1**: Lower motor neuron signs in legs, perianal numbness, increased tendon reflexes below lesion level.

Diagnosis

- **MRI of the vertebral column** is the gold standard for detecting vertebral collapse or metastatic disease.

Management

- **Immediate Treatment**:
  - **Dexamethasone** (16 mg STAT, followed by 8 mg twice daily [BD], oral or IV) to reduce tumor-related edema and improve neurological deficits.
- **Urgent Oncological Assessment**:
  - **Radiotherapy**:
    - Effective in **90%** of cases diagnosed early.
    - Immediate for lesions **above L1**, urgent for **L1 and below**.
  - **Spinal Stabilization Surgery**:
    - Consider for **structural spinal failure** or **mechanical pain** not relieved by analgesics.
    - Avoid **preoperative radiotherapy**; postoperative radiotherapy can be given after wound healing.

Disc prolapse

Definition

- **Disc prolapse** (herniated or slipped disc) occurs when the nucleus pulposus protrudes through the annulus fibrosus of an intervertebral disc, compressing adjacent nerve roots or the spinal cord.

Epidemiology

- Common in adults aged **30-50 years**.
- Often affects the **lumbar spine** (L4-L5, L5-S1) but can also occur in the **cervical spine**.

Pathophysiology

- Degenerative changes in the disc lead to a weakened annulus fibrosus.
- Increased intra-disc pressure (e.g., due to lifting, bending) pushes the nucleus pulposus outward, causing nerve compression.

Clinical Features

- **Lower back pain**: Sudden onset, often radiating to the buttocks and legs (sciatica).
- **Radicular pain**: Sharp, shooting pain following the path of the affected nerve (e.g., down the leg for lumbar prolapse).
- **Neurological deficits**:
  - **Sensory changes**: Numbness, tingling in the dermatome of the affected nerve root.
  - **Motor weakness**: Weakness in muscles innervated by the affected nerve.
  - **Reflex changes**: Reduced or absent deep tendon reflexes.
- **Cauda equina syndrome** (in severe cases):
  - Saddle anesthesia, bowel or bladder dysfunction, and reduced perianal reflexes (requires immediate medical attention).

Diagnosis

- **Clinical assessment**:
  - History and physical examination, including the **straight leg raise (SLR) test** for lumbar disc prolapse.
- **Imaging**:
  - **MRI**: Modality of choice for visualizing disc herniation and nerve root compression.
  - **CT scan**: Alternative if MRI is contraindicated.

Management

- **Conservative treatment**:
  - **Rest and activity modification**: Avoid heavy lifting and prolonged sitting.
  - **Analgesics**: NSAIDs (e.g., ibuprofen 400-800 mg TID) for pain relief.
  - **Physical therapy**: Strengthening and stretching exercises for the lower back.
- **Pharmacological**:
  - **Muscle relaxants** (e.g., diazepam 2-5 mg TID) for short-term relief of muscle spasm.
- **Interventional treatment**:
  - **Epidural steroid injections**: To reduce inflammation and pain.
- **Surgical intervention**:
  - **Discectomy**: Indicated for persistent pain or neurological deficits not responding to conservative treatment or for emergency conditions like cauda equina syndrome.

Complications

- **Chronic pain**: May persist even after treatment.
- **Permanent neurological deficits**: In cases of severe or untreated nerve compression.
- **Recurrent herniation**: Can occur at the same or different levels.

Features of Spinal Compression by Level

Level of Compression	Motor Deficits	Sensory Deficits	Reflex Changes	Associated features
Cervical Spine (C1-C7)	Weakness in upper limbs and possibly lower limbs (quadriparesis in severe cases)	Numbness/tingling in upper limbs, neck, and shoulders	Hyperreflexia in upper and lower limbs	Possible respiratory involvement (C3-C5: phrenic nerve)
Thoracic Spine (T1-T12)	Weakness/paralysis in the trunk and lower limbs (paraplegia)	Sensory loss below the level of compression (band-like distribution)	Hyperreflexia in lower limbs	Gait disturbances, autonomic dysfunction (e.g., bowel/ bladder)
Lumbar Spine (L1-L5)	Weakness in lower limbs (distal more affected, e.g., foot drop)	Sensory changes in lower limbs, especially anterior and medial thighs	Reduced/ absent patellar reflex (L4)	Radicular pain (e.g., sciatica), lower back pain

Level of Compression	Motor Deficits	Sensory Deficits	Reflex Changes	Associated features
Sacral Spine (S1-S5)	Weakness in lower limbs (e.g., difficulty with plantar flexion)	Sensory loss in the posterior legs and perineum (saddle anesthesia)	Reduced/ absent Achilles reflex (S1)	Bowel and bladder dysfunction, sexual dysfunction
Cauda Equina	Flaccid paralysis/weakness in lower limbs	Sensory loss in the perineum (saddle anesthesia) and lower limbs	Absent reflexes in lower limbs (areflexia)	Severe lower back pain, bowel/ bladder incontinence, urgent surgical intervention required

Prolapsed cervical disc (Cervical radiculopathy)

Prolapsed Cervical Disc (Cervical Radiculopathy)

Definition

- **Cervical radiculopathy** is a condition caused by the compression or irritation of a cervical nerve root due to a prolapsed intervertebral disc, resulting in pain, weakness, or sensory changes in the upper limb.

Epidemiology

- Most common in **middle-aged adults** (40-50 years).
- Frequently affects the **C5-C6** and **C6-C7** levels.

Pathophysiology

- **Degenerative changes** in the cervical spine lead to disc herniation or bulging, compressing adjacent nerve roots.
- This results in nerve inflammation and impaired nerve function, leading to radicular pain and neurological deficits.

Clinical Features

- **Neck pain**: May radiate to the shoulder, arm, or hand.
- **Radicular pain**: Sharp, shooting pain along the distribution of the affected nerve.
- **Paresthesia**: Tingling or numbness in the dermatome of the affected nerve root.
- **Muscle weakness**: Specific to muscles innervated by the compressed nerve.
- **Reflex changes**: Diminished or absent reflexes corresponding to the affected nerve root.
- **Common levels and associated signs**:
  - **C5-C6 (C6 root)**: Pain radiating to the thumb, weakness in the biceps, and diminished biceps reflex.
  - **C6-C7 (C7 root)**: Pain radiating to the middle finger, weakness in triceps, and reduced triceps reflex.

Diagnosis

- **Clinical assessment**:
  - History and physical examination with **Spurling's test** to reproduce radicular pain.
- **Imaging**:
  - **MRI**: Modality of choice to visualize disc prolapse and nerve root compression.
  - **CT myelography**: Alternative when MRI is contraindicated.

- **Electrodiagnostic studies**:
  - **Nerve conduction studies (NCS)** and **electromyography (EMG)** to confirm the diagnosis and rule out peripheral nerve conditions.

Management

- **Conservative treatment**:
  - **Analgesics**: NSAIDs (e.g., ibuprofen 400-800 mg TID).
  - **Physical therapy**: Strengthening and stretching exercises for the neck.
  - **Cervical collar**: Short-term use to immobilize and reduce movement.
- **Pharmacological management**:
  - **Muscle relaxants** (e.g., cyclobenzaprine 5-10 mg TID) for muscle spasm.
  - **Oral corticosteroids** (e.g., prednisone tapering dose) for significant inflammation.
- **Interventional treatment**:
  - **Cervical epidural steroid injections** to reduce inflammation and pain.
- **Surgical intervention**:
  - **Anterior cervical discectomy and fusion (ACDF)** or **cervical disc replacement** indicated for persistent pain, progressive neurological deficits, or failure of conservative treatment.

Lumbosacral plexopathy

Aspect	Details
Definition	Lumbosacral plexopathy refers to damage or dysfunction of the lumbosacral plexus, leading to motor and sensory deficits in the lower extremities and pelvis.
Nerve Roots Involved	L1–S4
Common Causes	Trauma (e.g., pelvic fractures), compression (e.g., tumors, hematomas, abscesses), diabetic amyotrophy, post-radiation plexopathy, obstetric complications.
Clinical Features	Unilateral or bilateral leg weakness, numbness, and tingling; muscle atrophy; pain in the hip, buttocks, or thigh; impaired reflexes depending on the specific roots affected.
Motor Deficit	Weakness can involve hip flexion, extension, abduction, adduction, knee extension, and foot movements (dorsiflexion, plantarflexion).
Sensory Deficit	Reduced sensation over the anterior, medial, or lateral thigh, medial leg, and parts of the foot, depending on the nerve roots affected.
Associated Features	May include bladder and bowel dysfunction if autonomic fibers are involved.
Diagnostic Tests	MRI of the pelvis and lumbosacral spine, EMG/NCS to assess nerve conduction and muscle involvement, CT scans for detecting masses or structural causes.
Differentiating Features	Distinguishable from lumbosacral radiculopathy by the extent of involvement (plexopathy affects multiple nerve roots rather than a single nerve root).
Treatment	Depends on the underlying cause: conservative management (e.g., physical therapy, pain control), surgical intervention for compression or mass lesions, and management of associated conditions (e.g., diabetes control).

Conus medullaris and cauda equina syndromes

Feature	Conus Medullaris Syndrome	Cauda Equina Syndrome
Anatomical Location	Injury to the **conus medullaris** (terminal end of the spinal cord)	Injury to the **cauda equina** (bundle of nerve roots below the conus)
Etiology	Commonly due to spinal trauma, tumors, disc herniation at **L1-L2**	Often caused by large **lumbar disc herniation**, tumors, trauma, or abscess
Onset	Typically **sudden and bilateral**	**Gradual and unilateral** (can become bilateral if severe)
Motor Deficits	Weakness is more **symmetrical**, affecting the lower limbs	Weakness is typically **asymmetrical** and affects specific myotomes
Sensory Deficits	Sensory loss in a **saddle distribution** (perianal area and inner thighs)	Sensory loss in a **saddle distribution** with potential involvement of lower limb dermatomes
Reflex Changes	**Knee and ankle reflexes** may be diminished or absent	**Ankle reflexes** more commonly affected; knee reflexes may be spared
Bowel and Bladder Dysfunction	**Early** presentation of bowel and bladder dysfunction (e.g., retention, incontinence)	**Late** presentation of bowel and bladder dysfunction
Sexual Dysfunction	Frequently present and may be severe	May be present but less pronounced compared to conus medullaris syndrome
Pain	**Lower back pain** may be less severe; bilateral and poorly localized	**Severe radicular pain**, typically unilateral, sharp, and well-localized
Neurological Signs	Combination of **upper and lower motor neuron signs**	**Lower motor neuron signs** (e.g., areflexia, flaccid paralysis)
Prognosis	Often less favorable due to earlier bowel and bladder involvement	Prognosis can be better if treated promptly, but recovery varies
Management	**Emergency MRI** to identify compression; urgent surgical decompression	**Emergency MRI** and surgical decompression are critical to prevent permanent deficits

Key Differences

- **Conus medullaris syndrome** presents with **mixed upper and lower motor neuron** signs and earlier bowel/bladder involvement, typically bilateral.
- **Cauda equina syndrome** involves **purely lower motor neuron signs**, is often **asymmetrical**, and bowel/bladder symptoms appear later.

Key Points

- **Both syndromes are neurological emergencies** requiring immediate evaluation and intervention.
- **MRI** is the imaging of choice to identify the level and cause of compression.

Subacute combined degeneration of spinal cord (SACDC)

Definition

- SACDC is a progressive, neurological condition characterized by the degeneration of the posterior and lateral columns of the spinal cord due to vitamin B12 deficiency (cobalamin deficiency).

Pathophysiology

- Vitamin B12 is essential for myelin synthesis. Its deficiency leads to demyelination, primarily affecting the dorsal (posterior) columns and the corticospinal tracts in the spinal cord.
- Myelin damage impairs both sensory and motor pathways, leading to combined symptoms.

Causes

- **Dietary Deficiency**: Insufficient intake of vitamin B12 (e.g., vegan diet without supplementation).
- **Malabsorption**:
  - Pernicious anemia (autoimmune destruction of gastric parietal cells leading to reduced intrinsic factor production).
  - Gastrointestinal surgeries (e.g., gastrectomy, ileal resection).
  - Conditions affecting the ileum (e.g., Crohn's disease).
- **Other Factors**: Chronic use of certain medications (e.g., metformin, proton pump inhibitors) can impair B12 absorption.

Clinical Features

- **Sensory Symptoms**:
  - Paresthesia (tingling, numbness) in hands and feet.
  - Loss of proprioception and vibration sense, often resulting in an unsteady gait (sensory ataxia).
- **Motor Symptoms**:
  - Spasticity and muscle weakness due to corticospinal tract involvement.
  - Hyperreflexia (increased deep tendon reflexes) and positive Babinski sign.
- **Neuropsychiatric Symptoms**:
  - Cognitive disturbances, irritability, and depression.
- **Other Findings**:
  - Glossitis (smooth, red tongue).
  - Peripheral neuropathy.

Diagnosis

- **Blood Tests**:
  - Low serum vitamin B12 levels.
  - Elevated methylmalonic acid (MMA) and homocysteine levels (more sensitive indicators of B12 deficiency).
- **Complete Blood Count (CBC)**:
  - May show macrocytic anemia with hypersegmented neutrophils.
- **MRI of the Spine**:
  - Hyperintense signals in the posterior and lateral columns on T2-weighted images.
- **Schilling Test** (historical): Previously used to diagnose pernicious anemia.

Management

- **Vitamin B12 Replacement**:
  - Initial treatment with intramuscular B12 injections (e.g., 1,000 mcg daily for 1-2 weeks, followed by weekly, then monthly).

- **Oral Supplementation**:
  - May be used for maintenance once levels stabilize and absorption issues are corrected.
- **Treat Underlying Causes**:
  - Manage any gastrointestinal disorders or medication-related issues affecting B12 absorption.

Prognosis

- **Early Treatment**: Can lead to significant improvement or complete reversal of neurological symptoms.
- **Delayed Treatment**: Permanent neurological deficits may remain if treatment is delayed or if degeneration is severe.

Syringomyelia

Definition: Syringomyelia is a chronic, progressive condition characterized by the development of a fluid-filled cyst (syrinx) within the spinal cord, leading to tissue damage and neurological symptoms.

Pathophysiology:

- The syrinx expands and elongates over time, damaging the spinal cord.
- Commonly associated with conditions such as Chiari malformations (Type I), trauma, tumors, or arachnoiditis.
- Disrupts the decussating fibers of the spinothalamic tract, affecting pain and temperature sensation.

Causes:

- Congenital (e.g., Chiari malformation Type I)
- Acquired (e.g., spinal cord trauma, tumors, meningitis, post-inflammatory arachnoiditis)

Clinical Features:

- **Sensory Symptoms**:
  - Loss of pain and temperature sensation in a "cape-like" distribution across the shoulders, arms, and back (spinothalamic tract involvement).
  - Preservation of light touch and proprioception.
- **Motor Symptoms**:
  - Muscle weakness and atrophy, particularly in the hands and arms (lower motor neuron signs).
  - Spasticity and hyperreflexia in later stages if corticospinal tracts are affected.
- **Autonomic Symptoms**:
  - Horner's syndrome if the syrinx extends into the cervical region.
  - Impaired bowel and bladder function in advanced cases.

Diagnosis:

- **Magnetic Resonance Imaging (MRI)**:
  - The gold standard for visualizing the syrinx and associated spinal cord abnormalities.
  - Identifies the extent of the syrinx and potential underlying causes (e.g., Chiari malformation).
- **Neurological Examination**:
  - Focuses on assessing sensory deficits, motor weakness, and reflex changes.

Treatment:

- **Surgical Intervention**:
  - **For Chiari malformation-associated syringomyelia**: Posterior fossa decompression to improve CSF flow.
  - **Shunt placement**: Syrinx-subarachnoid or syrinx-peritoneal shunt in selected cases.
- **Conservative Management**:
  - Observation for asymptomatic or stable cases.
- **Symptomatic Treatment**:
  - Pain management, physical therapy, and rehabilitation to address muscle weakness and maintain function.

Complications:

- Progressive spinal cord damage leading to permanent neurological deficits.
- Scoliosis, particularly in pediatric cases.
- Chronic pain and disability if untreated.

Syringomyelia, an enlargement of the central canal of the spinal cord, commonly occurs at C8-T1. Patients present with loss of pain and temperature sensation but normal position and vibration sensation.

Anterior spinal artery thrombosis

Definition:

- A rare condition involving occlusion of the anterior spinal artery, leading to ischemia of the anterior two-thirds of the spinal cord.

Pathophysiology:

- The anterior spinal artery supplies the anterior portion of the spinal cord, which includes the corticospinal tracts and spinothalamic tracts.
- Thrombosis leads to impaired blood flow, causing infarction and loss of function in these areas, sparing the dorsal columns.

Causes:

- Atherosclerosis
- Aortic surgery or dissection
- Embolic events
- Trauma or severe hypotension
- Vasculitis

Clinical Features:

- **Sudden onset of symptoms**, usually after an inciting event (e.g., surgery, hypotension).
- **Motor Dysfunction**:
  - Acute flaccid paralysis below the level of the lesion (bilateral).
  - Progresses to spasticity over time (upper motor neuron signs).
- **Sensory Loss**:
  - Loss of pain and temperature sensation below the level of the lesion (due to spinothalamic tract involvement).
  - Preservation of proprioception and vibration (dorsal columns spared).
- **Autonomic Dysfunction**:
  - Urinary and bowel incontinence due to involvement of autonomic pathways.
  - Possible sexual dysfunction.

Diagnosis:

- **Clinical Assessment**:
  - Acute, symmetric motor and sensory deficits that align with anterior spinal artery distribution.
- **Magnetic Resonance Imaging (MRI)**:
  - Confirms spinal cord infarction and rules out other potential causes.
  - Shows characteristic changes in the anterior spinal cord.
- **CT Angiography or MR Angiography**:
  - Used to visualize the vascular supply and confirm the presence of thrombosis or other vascular abnormalities.

Management:

- **Immediate Supportive Care**:
  - Stabilize blood pressure and ensure adequate perfusion to prevent worsening ischemia.
- **Anticoagulation Therapy**:
  - May be considered in cases with an embolic or thrombotic cause, although evidence is limited.
- **Rehabilitation**:
  - Physical therapy for motor recovery.
  - Occupational therapy for adaptation and independence.
- **Symptomatic Treatment**:
  - Pain management.
  - Bladder and bowel care to manage autonomic dysfunction.

Incomplete spinal cord syndromes

Types of incomplete spinal cord syndromes

Type of Incomplete Spinal Cord Syndrome	Definition	Features	Causes	Treatment
Central Cord Syndrome	Damage primarily in the center of the spinal cord	Greater weakness in the upper limbs than lower limbs, possible bladder dysfunction, variable sensory loss	Hyperextension injuries, cervical spondylosis	Supportive care, physical therapy, surgical decompression if severe
Anterior Cord Syndrome	Damage to the anterior two-thirds of the spinal cord	Loss of motor function and pain/temperature sensation below the level of injury, preserved proprioception and vibration sense	Anterior spinal artery thrombosis, trauma, disc herniation	High-dose corticosteroids (controversial), surgical intervention, supportive care

Type of Incomplete Spinal Cord Syndrome	Definition	Features	Causes	Treatment
Brown-Séquard Syndrome	Hemisection of the spinal cord	Ipsilateral loss of motor function and proprioception/vibration, contralateral loss of pain and temperature sensation	Penetrating trauma, spinal cord tumors	Surgical decompression or repair, physical rehabilitation, supportive care
Posterior Cord Syndrome	Damage to the dorsal columns of the spinal cord	Loss of proprioception and vibration sense below the level of injury, preserved motor and pain/temperature sensation	Trauma, multiple sclerosis, vitamin B12 deficiency	Address underlying cause, supportive care, physical therapy
Conus Medullaris Syndrome	Injury to the conus medullaris (end of the spinal cord)	Symmetrical lower limb motor weakness, saddle anesthesia, early bladder and bowel dysfunction	Lumbar spinal injuries, tumors, disc herniation	Surgical decompression, pain management, physical rehabilitation
Cauda Equina Syndrome	Injury to the lumbosacral nerve roots (not true spinal cord)	Asymmetrical motor weakness, severe radicular pain, saddle anesthesia, late bladder/bowel dysfunction	Disc herniation, trauma, tumors	Emergency surgical decompression, pain control, physical therapy

Diagnosis

- Spinal MRI (best confirmatory test): excludes soft-tissue lesions (e.g., tumors, hematomas), bone lesions, and detects spinal cord parenchyma abnormalities (e.g., infarction

Myotonic dystrophy

Definition

- **Myotonic dystrophy (dystrophia myotonica)** is an inherited myopathy characterized by selective atrophy of type I muscle fibers, affecting skeletal, cardiac, and smooth muscles.

Genetics

- **Inheritance**: Autosomal dominant, **trinucleotide repeat disorder** in the **myotonin protein kinase gene**.
- **Types**:
  - **DM1 (Type 1)**: Mutation in the **DMPK gene** on chromosome **19**.
  - **DM2 (Type 2)**: Mutation in the **ZNF9 gene** on chromosome **3**.

Types of Myotonic Dystrophy

Type	Genetics	Onset	Features	Severity
DM1	**DMPK gene** on chromosome 19	Congenital, juvenile, adult	Distal weakness prominent	Severe
DM2	**ZNF9 gene** on chromosome 3	Adulthood	Proximal weakness prominent	Mild

Clinical Features

- **Age of Onset**: Usually between **20-40 years**.
- **Muscular**:
  - **Myotonic facies**: Long, 'haggard' appearance, frontal balding, atrophy of the **temporalis**, **masseters**, and facial muscles; **bilateral ptosis**.
  - **Myotonia**: Notable as a slow-relaxing grip, observed in a handshake.
  - **Weakness**: Typically starts distally in the arms and legs.
- **Other Systems**:
  - **Speech**: Dysarthria due to tongue and pharyngeal myotonia.
  - **CNS**: Mild mental impairment.
  - **Endocrine**: Insulin resistance leading to **diabetes mellitus**.
  - **Ophthalmologic**: Early-onset **cataracts**.
  - **Reproductive**: **Testicular atrophy**.
  - **Cardiac**: **Heart block**, **cardiomyopathy**.
  - **Swallowing**: **Dysphagia**.

Diagnosis

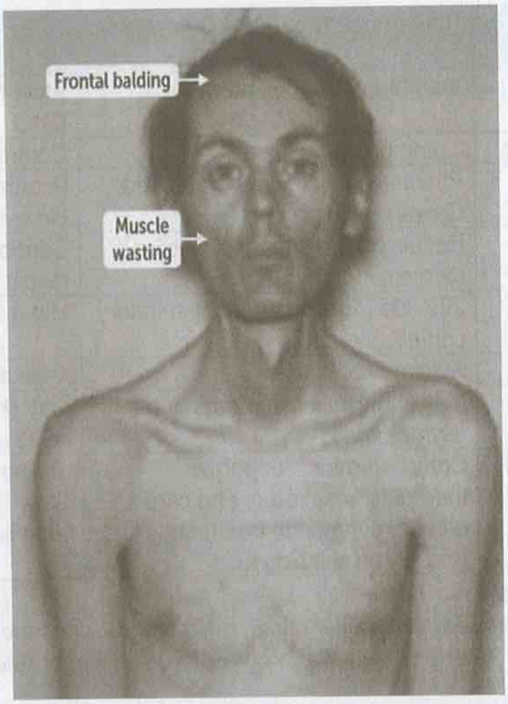
- **Serology**: Elevated serum **CK**.
- **Electromyography (EMG)**:
  - Reveals characteristic **waxing and waning potentials** termed the **"dive bomber effect"**.
- **Muscle Biopsy**: Used to assess structural muscle changes.
- **Genetic Testing**: The **gold standard** for confirming the diagnosis.

Treatment

- **Symptomatic management**:
  - **Weakness**: No definitive treatment available.
  - **Myotonia**:
    - **Phenytoin (100-300 mg/day)**, **quinine (300 mg TID)**, or **procainamide**; **mexiletine (150-200 mg TID)** may also be used.
  - **Cardiac Abnormalities**: Pacemaker insertion for heart block.
  - **Sleep Apnea**: Managed with **CPAP**.
  - **Foot Drop**: Use of **ankle-foot orthosis and splints**.
  - **Ptosis**: **Lid-lifting surgery** considered only in severe cases.
  - **Cataracts**: May require surgical extraction.
- **Supportive care**:
  - **Genetic counseling and testing** for patients and family members.

Prognosis

- The course is **chronic and progressive**.
- **Cardiac complications** significantly reduce life expectancy.



Dystrophinopathies

Comparison: Duchenne Muscular Dystrophy (DMD) vs. Becker Muscular Dystrophy (BMD)

Characteristic	Duchenne Muscular Dystrophy (DMD)	Becker Muscular Dystrophy (BMD)
Definition	A severe X-linked recessive disorder characterized by progressive muscle degeneration due to complete loss of functional dystrophin.	A milder X-linked recessive disorder characterized by progressive muscle degeneration due to partially functional dystrophin.
Mechanism	Caused by mutations in the *DMD* gene that result in little to no production of dystrophin, leading to muscle fiber damage and degeneration.	Caused by mutations in the *DMD* gene that result in an abnormal but partially functional dystrophin protein, leading to slower muscle degeneration.
Severity	Severe	Milder
Onset Age	Early childhood (typically 3-5 years)	Later childhood to adolescence
Progression	Rapid	Slower, more gradual
Ambulation	Loss by early teens (usually by age 12)	Retained into late teens or adulthood
Genetic Mutation	Complete loss or nonfunctional dystrophin	Partially functional dystrophin

Characteristic	Duchenne Muscular Dystrophy (DMD)	Becker Muscular Dystrophy (BMD)
Creatine Kinase (CK) Levels	Very high (10-100x normal)	Elevated but typically lower than DMD
Cardiomyopathy	Common, early onset	Common, but typically later onset
Muscle Involvement	Proximal muscles more affected; Gowers' sign present	Proximal muscle weakness; Gowers' sign may be present
Complications	Respiratory failure, scoliosis, cardiomyopathy	Cardiomyopathy, less severe respiratory issues
Life Expectancy	20s-30s (due to cardiac/respiratory complications)	Mid-adulthood or beyond, variable
Inheritance	X-linked recessive	X-linked recessive
Carrier Female Symptoms	May show mild symptoms or be asymptomatic	May show very mild symptoms or be asymptomatic
Management	Corticosteroids, supportive therapies, respiratory and cardiac care, experimental treatments (e.g., exon skipping)	Similar management, tailored to slower progression and delayed complications

Key Differences:

- **DMD**: More severe with earlier onset, rapid progression, and earlier loss of ambulation.
- **BMD**: Milder, later onset, slower progression, and longer retention of muscle function and ambulation.

Shared Features:

- Both conditions result from mutations in the *DMD* gene on the X chromosome, impacting dystrophin, a protein crucial for muscle fiber integrity.
- Both present with proximal muscle weakness and share an X-linked recessive inheritance pattern, primarily affecting males.

Hypokalaemic periodic paralysis and thyrotoxic periodic paralysis

Epidemiology

- More common in **Asian men** aged **30-50 years**.
- Higher prevalence in patients with **thyrotoxicosis** of **Chinese origin** (13-14%) compared to **Caucasians** (0.1-0.2%).
- Occurs in approximately **10%** of young Latin American or Asian men with thyrotoxicosis.

Pathophysiology

- **Autosomal dominant disorder** with mutations in **muscle voltage-gated calcium channels**.
- Increased **Na+/K+-ATPase activity** leads to **shift of potassium into tissues**, causing hypokalaemia and muscle weakness.

Clinical Features

- **Episodes of Paralysis**:
  - **Sudden onset** of complete weakness with rapid recovery.
  - **Focal or generalized flaccid muscle weakness** (periodic paralysis).
  - **Proximal muscles** are predominantly affected; **respiratory and facial muscles** are usually spared.
  - Episodes last **hours to days**.

   - Accompanied by **fatigue, muscle pain**, and/or altered consciousness during attacks.
   - **Normal neurological examination** between episodes.
- **Triggers**:
   - **Carbohydrate-rich meals**.
   - **Exercise**.
   - **Stress**.
- **Association with Thyrotoxicosis**:
   - **Thyrotoxic periodic paralysis** (when associated with hyperthyroidism).
   - **Hypokalaemic periodic paralysis** (when not associated with hyperthyroidism).

Diagnosis

- **Laboratory findings**:
   - ↓ **Potassium (K+)** during an attack.
   - ↓ **TSH**, ↑ **T3 and T4** in cases of **thyrotoxic periodic paralysis**.
- **Clinical documentation** of hypokalaemia and related symptoms during an attack confirms the diagnosis.

Management

- **Acute Treatment**:
   - **Potassium infusion** provides immediate relief from paralysis.
   - **Continuous cardiac monitoring** to detect potential arrhythmias.
- **Long-term Management**:
   - **Lifelong potassium supplementation** may be required.
   - **Non-selective beta-blockers** (e.g., **propranolol** 10-40 mg TID) to reduce hyperadrenergic stimulation of **Na+/K+-ATPase**.
- **Thyrotoxic periodic paralysis**:
   - **Treat the underlying thyrotoxicosis** to resolve periodic paralysis episodes.

Neuromyelitis optica (NMO)

Definition

- **Neuromyelitis optica (NMO)**, also known as **Devic's disease**, is an autoimmune demyelinating disorder of the central nervous system primarily affecting the **optic nerves** and **spinal cord**, leading to **optic neuritis** and **transverse myelitis**.

Pathophysiology

- **Autoimmune** condition involving antibodies against **aquaporin-4** (AQP4), the main water channel protein found on astrocytes.
- The binding of AQP4 antibodies induces **inflammatory damage** to the optic nerves and spinal cord.

Epidemiology

- More common in **women** than men.
- Often presents between **30-50 years** of age.

Clinical Features

- **Optic Neuritis**:
   - **Sudden vision loss** in one or both eyes.
   - Pain with eye movement.
- **Transverse Myelitis**:
   - **Weakness** or paralysis in the legs or arms.

  - **Sensory changes** such as numbness or tingling.
  - **Bowel and bladder dysfunction**.
  - **Severe back pain** in some cases.
- **Systemic Features**:
  - Nausea, vomiting, and hiccups due to involvement of the area postrema in the brainstem.

Diagnosis

- **Clinical assessment**:
  - History and neurological examination focusing on visual and spinal cord symptoms.
- **Imaging**:
  - **MRI**: Lesions extending over **three or more vertebral segments** in the spinal cord; optic nerve enhancement.
- **Serological Tests**:
  - **NMO-IgG/AQP4 antibody**: Highly specific for NMO.
- **CSF analysis**:
  - May show elevated **protein** and **pleocytosis**.
  - **Oligoclonal bands** usually absent, distinguishing it from **multiple sclerosis (MS)**.

Differentiation from Multiple Sclerosis (MS)

- **NMO** typically involves **longer spinal cord lesions** (>3 vertebral segments).
- **MS** often presents with **brain lesions** that follow the McDonald criteria and shorter spinal cord involvement.
- **NMO-IgG/AQP4 antibody** testing is positive in NMO but not in MS.

Treatment

- **Acute management**:
  - **High-dose intravenous corticosteroids** (e.g., methylprednisolone 1 g/day for 3-5 days).
  - **Plasma exchange (PLEX)** for cases not responding to steroids.
- **Long-term immunosuppression**:
  - **Azathioprine (2-3 mg/kg/day), mycophenolate mofetil (1-2 g/day), or rituximab (375 mg/m² weekly for 4 weeks or 1 g every 6 months).**

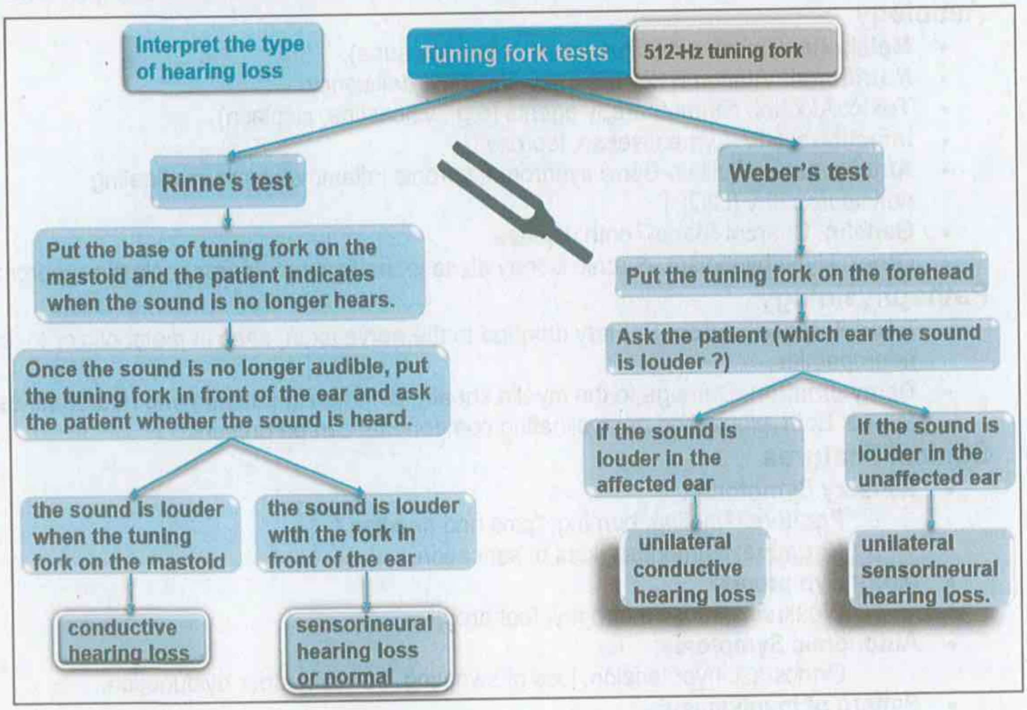
Hearing loss

Hearing Loss: Conductive vs. Sensorineural

Feature	Conductive Hearing Loss	Sensorineural Hearing Loss
Age of Onset	Commonly in **childhood or young adulthood**	Commonly in **middle or late age**
Aetiology	- **Otosclerosis** - **Otitis media** - **Ear barotrauma** - **Cerumen impaction** - **External auditory canal atresia**	- **Ménière's disease** - **Acoustic neuroma** - **Noise-induced hearing loss** - **Internal ear infections** - **Presbycusis**
Pathophysiology	**External or middle ear pathology** disrupting sound conduction to the inner ear	**Inner ear, cochlear, or auditory nerve pathology** impairing neuronal transmission to the brain

Feature	Conductive Hearing Loss	Sensorineural Hearing Loss
Clinical Features	- **Hearing improves** in noisy environments - **Normal voice volume** - Sound is usually not distorted - **Features of external ear pathology** (e.g., cerumen impaction)	- **Hearing worsens** in noisy environments - **Loud voice volume** (due to impaired nerve transmission) - **Loss of higher frequencies**, distorted sounds - **Absent external ear pathology**
Weber Test (unilateral hearing loss)	**Lateralization to impaired ear** (reduced ambient noise allows better detection of vibration)	**Lateralization to good ear** (inner ear or nerve damage impairs sound transmission)
Rinne Test (unilateral hearing loss)	**Bone conduction > air conduction** (vibrations bypass blockage and reach cochlea)	**Air conduction > bone conduction** (inner ear/nerve damage prevents proper sound transmission)

Rinne's and Weber's test



Peripheral neuropathy

Definitions

- **Peripheral neuropathy** refers to damage or dysfunction of peripheral nerves, leading to sensory, motor, or autonomic impairments.
- **Allodynia**: **pain** caused by a **stimulus** that does not normally cause pain (e.g. light touch, contact with clothing)
- **Dysesthesia**: abnormal **spontaneous** sensations (burning, stinging, stabbing) **from activities** that do not normally cause pain)
- **Paresthesia**: an abnormal skin sensation **in the absence of a stimulus** (described as burning, prickling, itching, tingling)
- **Hyperesthesia**: increased sensitivity to sensory stimuli
- **Hypoesthesia**: decreased sensitivity to sensory stimuli

Types

- **Mononeuropathy**: Damage to a single peripheral nerve (e.g., carpal tunnel syndrome).
- **Polyneuropathy**: Damage to multiple peripheral nerves, typically symmetric.
- **Mononeuritis multiplex**: Damage to two or more nerves in separate areas of the body.

Aetiology

- **Metabolic**: Diabetes mellitus (most common cause).
- **Nutritional**: Vitamin B12 deficiency, thiamine deficiency.
- **Toxic**: Alcohol, chemotherapy agents (e.g., vincristine, cisplatin).
- **Infectious**: HIV, Lyme disease, leprosy.
- **Autoimmune**: Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP).
- **Genetic**: Charcot-Marie-Tooth disease.
- **Other**: Hypothyroidism, chronic kidney disease, malignancy (paraneoplastic syndrome).

Pathophysiology

- **Axonal degeneration**: Primary damage to the nerve axon, seen in metabolic or toxic neuropathies.
- **Demyelination**: Damage to the myelin sheath, common in autoimmune neuropathies.
- **Mixed**: Both axonal and demyelinating components can be present.

Clinical Features

- **Sensory Symptoms**:
  - **Positive**: Tingling, burning, "pins and needles."
  - **Negative**: Numbness, loss of sensation.
- **Motor Symptoms**:
  - Weakness, muscle atrophy, foot drop.
- **Autonomic Symptoms**:
  - Orthostatic hypotension, loss of sweating, bowel/bladder dysfunction.
- **Pattern of Involvement**:
  - **Stocking-glove pattern**: Common in polyneuropathy, with symptoms starting in the distal extremities.

Diagnosis

- **Clinical assessment**:
  - Comprehensive history and physical examination to identify the pattern and potential underlying causes.
- **Electrodiagnostic studies**:

- Nerve conduction studies (NCS) and electromyography (EMG) to differentiate between axonal and demyelinating neuropathies.

• **Laboratory tests**:
  - Blood glucose, HbA1c, vitamin B12 levels, thyroid function tests, renal function.
• **Additional tests**:
  - **CSF analysis** for suspected autoimmune neuropathies.
  - **Genetic testing** if a hereditary neuropathy is suspected.

Management

• **Underlying cause**:
  - **Diabetes management**: Optimize glycemic control.
  - **Nutritional**: Vitamin supplementation (e.g., vitamin B12 injections).
  - **Toxic**: Removal of the offending agent (e.g., reduce alcohol intake, switch chemotherapy drugs).
• **Symptomatic treatment**:
  - **Pain management**:
    - **First-line**: Gabapentin (300-900 mg/day), pregabalin (75-300 mg/day), amitriptyline (10-50 mg/day).
    - **Alternative**: Duloxetine (30-60 mg/day), carbamazepine.
  - **Physical therapy**: To maintain muscle strength and prevent atrophy.
  - **Orthotics**: For foot drop or gait instability.

Complications

• **Ulcers and infections**: Due to loss of sensation, particularly in diabetic patients.
• **Falls and fractures**: From motor weakness and proprioceptive loss.
• **Chronic pain**: Can lead to decreased quality of life and potential mental health issues.

Causes of Peripheral Neuropathy and Diagnostic Features

Cause	Type	Diagnostic Features
Diabetes Mellitus	Metabolic	Elevated **HbA1c** and **blood glucose** levels; **symmetric sensory loss** in a stocking-glove pattern; nerve conduction studies showing **axonal degeneration**
Vitamin B12 Deficiency	Nutritional	Low **serum vitamin B12**; macrocytic anemia; **paresthesia**, ataxia, and possible cognitive changes; nerve conduction studies showing **demyelination**
Alcohol Use	Toxic	History of chronic alcohol consumption; **symmetrical distal sensory loss**; nerve conduction studies showing **axonal degeneration**
Chemotherapy Agents	Toxic	History of exposure to neurotoxic drugs (e.g., vincristine, cisplatin); sensory and motor findings, often **symmetric**; nerve conduction studies showing **axonal loss**
HIV Infection	Infectious	Positive **HIV serology**; distal sensory polyneuropathy; nerve conduction studies showing **mixed axonal and demyelinating features**

Cause	Type	Diagnostic Features
Lyme Disease	Infectious	Positive **Lyme serology**; **radiculopathy** or mononeuropathy multiplex; CSF analysis may show **pleocytosis**
Guillain-Barré Syndrome (GBS)	Autoimmune	Recent infection or vaccination; **ascending weakness**, hyporeflexia; nerve conduction studies showing **demyelination**; elevated **CSF protein** without pleocytosis
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Autoimmune	Gradual onset weakness; **symmetric motor and sensory deficits**; nerve conduction studies showing **demyelination**; **CSF protein** elevation
Charcot-Marie-Tooth Disease	Genetic	Family history of neuropathy; **foot deformities** (e.g., pes cavus); nerve conduction studies showing **uniform slowing of conduction velocity**; genetic testing confirms diagnosis
Hypothyroidism	Metabolic	Elevated **TSH** and low **free T4**; **distal sensory loss**, fatigue; nerve conduction studies showing **axonal degeneration**
Chronic Kidney Disease	Metabolic	Elevated **urea and creatinine**; **symmetrical distal sensory loss**; nerve conduction studies showing **axonal degeneration**
Paraneoplastic Syndrome	Malignancy-related	Association with known malignancy; **subacute onset** of neuropathy; nerve conduction studies showing **mixed patterns**; positive **paraneoplastic antibodies**

Drugs causing peripheral neuropathy

- Antibiotics: nitrofurantoin, metronidazole
- Amiodarone
- **Isoniazid**
- Vincristine
- Tricyclic antidepressants

Critical illness polyneuropathy

- **Prolonged periods in the Intensive Therapy Unit, irrespective of the underlying pathology, are associated with a risk of developing critical illness polyneuropathy**
- **It is an axonal neuropathy and thus muscle wasting may occur**
- **May be predominantly sensory, predominantly motor or mixed**

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Overview

- CIDP is characterised by progressive weakness and impaired sensory function in the upper and lower limbs.
- **subacute** sensory and motor peripheral neuropathy
- The cause of the demyelination is not understood,
- More common in young adults and in men.
- mainly causes motor impairment (distal and proximal).
- **CIDP causes a large fibre peripheral neuropathy (Joint position sense and vibration are carried through large fibres)**

Features

- weakness of the limbs
- **areflexia**
- abnormal sensation (which typically begins distally)
- fatigue.
- **Autoantibodies against GM1 gangliosides**

Differential diagnosis

1. CIDP is closely linked to **Guillain-Barré syndrome (GBS**), and is thought by some to be its chronic counterpart.
   - ⇨ Both CIDP and GBS can affect motor and sensory nerves
   - ⇨ (GBS) is an **acute** (which reaches its peak in severity **within six weeks**), post-infectious neuropathy
   - ⇨ Whereas CIDP is **subacute (several months history)**
2. **Hereditary motor and sensory neuropathy (HMSN)** is normally a **very chronic** neuropathy developing **over many years** and usually with a family history of the condition.

Treatment

- Corticosteroids
- plasmapheresis
- Intravenous immunoglobulin
- Physiotherapy

> **Chronic inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barre** syndrome (hyporeflexia or areflexia, paraesthesia and mild sensory deficits in the upper and lower extremities, weakness) **except that it follows a chronic progressive course.**

Neuropathic pain

Aspect	Details
Definition	Chronic pain arising from **damage or dysfunction** of the nervous system, characterized by altered sensory processing.
Common Causes	- **Peripheral**: Diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, HIV-associated neuropathy, chemotherapy-induced neuropathy. - **Central**: Spinal cord injury, multiple sclerosis, stroke. - **Other**: Complex regional pain syndrome (CRPS), phantom limb pain.
Pathophysiology	- **Ectopic discharges**: Spontaneous pain signals from damaged nerves. - **Central sensitization**: Persistent stimulation causing exaggerated pain response.
Clinical Features	- **Spontaneous pain**: Burning, shooting, stabbing. - **Allodynia**: Pain from typically non-painful stimuli. - **Hyperalgesia**: Heightened response to painful stimuli. - **Paresthesia/Dysesthesia**: Abnormal sensations, tingling.
Diagnosis	- **Clinical history**: Identification of typical neuropathic pain features. - **Questionnaires**: NPQ, DN4. - **Physical exam**: Check for allodynia, hyperalgesia. - **Electrodiagnostic studies**: NCS, EMG. - **Lab tests**: Depending on suspected etiology (e.g., HbA1c, vitamin B12).
Pharmacological Treatment	- **First-line**: Gabapentin (300-1200 mg TID), pregabalin (150-600 mg/day), amitriptyline (10-75 mg/day), duloxetine (30-60 mg/day). - **Second-line**: Capsaicin cream, lidocaine patches, tramadol (50-100 mg q6h). - **Third-line**: Opioids (reserved for severe cases).
Non-Pharmacological Treatment	- **Physical therapy**: Maintains function. - **CBT**: For chronic pain management. - **TENS**: Pain relief in some cases.
Interventional Procedures	Nerve blocks, spinal cord stimulation for refractory cases.

Autonomic neuropathy

Aspect	Details
Definition	Damage to the **autonomic nerves** affecting involuntary bodily functions like heart rate, blood pressure, and digestion.
Common Aetiologies	- **Diabetes mellitus** (most common) - **Metabolic disorders**: Chronic kidney disease, vitamin B12 deficiency - **Autoimmune diseases**: Guillain-Barré syndrome, SLE - **Infections**: HIV, Lyme disease, Chagas disease - **Paraneoplastic syndromes** - **Hereditary**: Familial amyloid polyneuropathy - **Drug-induced**: Chemotherapy agents, antiretrovirals
Pathophysiology	Damage to **small nerve fibers** affecting the **sympathetic and parasympathetic systems**, leading to impaired regulation.
Clinical Features	- **Cardiovascular**: Orthostatic hypotension, resting tachycardia - **Gastrointestinal**: Gastroparesis, constipation, diarrhea - **Genitourinary**: Bladder dysfunction, erectile dysfunction - **Sudomotor**: Altered sweating - **Other**: Impaired pupillary response, temperature dysregulation
Diagnosis	- **Clinical assessment**: History and evaluation of symptoms - **Tilt-table test**: For orthostatic hypotension - **HRV**: For heart rate control assessment - **Gastric emptying study**: For suspected gastroparesis - **Lab tests**: Glucose, HbA1c, vitamin levels - **Nerve conduction studies**: If concurrent somatic neuropathy suspected
Management	- **Treat underlying cause**: Optimize glycemic control, supplement vitamins - **Symptomatic treatment**: • **Cardiovascular**: Fludrocortisone (0.1-0.3 mg/day), midodrine (2.5-10 mg TID) • **Gastrointestinal**: Prokinetics (e.g., metoclopramide 10 mg TID), laxatives • **Genitourinary**: Intermittent catheterization, PDE inhibitors • **Sudomotor**: Topical agents for hyperhidrosis - **Lifestyle adjustments**: Hydration, compression garments, small frequent meals
Complications	- **Falls/injuries** due to orthostatic hypotension - **UTIs** from incomplete bladder emptying - **Nutritional deficiencies**

Mononeuritis multiplex

Definition : ≥ 2 isolated mononeuropathies

Causes

- Axonal injury caused by damage to vasa nervorum
- Occurs in conditions characterized by the development of granulomas and/or microangiopathy (e.g., diabetes mellitus, rheumatoid arthritis, vasculitides, SLE, Lyme disease, amyloidosis, HIV, polyarteritis nodosa)

Features: painful, asymmetrical sensory and motor symptoms

Diagnosis: **Nerve biopsy should be performed to confirm the diagnosis**

Treatment: includes prednisolone and cyclophosphamide

Guillain-Barre syndrome(GPS) (also known as Post-infectious polyradiculopathy)

- **Definition:** Immune-mediated demyelination of the peripheral nervous system, often following an infection (e.g., *Campylobacter jejuni*, cytomegalovirus).
- **Pathogenesis:**
  - Cross-reaction of antibodies with gangliosides in the PNS.
  - Anti-GM1 antibodies found in 25% of patients.
- **Characteristic Features:**
  - Progressive, symmetrical limb weakness (ascending pattern, affects proximal muscles first).
  - Mild sensory symptoms (e.g., distal paraesthesia).
  - Areflexia.
  - Cranial nerve involvement (e.g., diplopia).
  - Bulbar involvement in 50% (risk of aspiration and respiratory insufficiency).
  - Autonomic dysfunction (e.g., urinary retention).
  - Muscle wasting in prolonged cases.
- **Less Common Findings:**
  - Papilloedema due to reduced CSF resorption.
- **Investigations:**
  - **CSF analysis**: Elevated protein, normal glucose, no pleocytosis (protein peak in the 2nd-3rd week).
  - **Nerve conduction studies**: Show demyelination.
  - **MRI**: Used to exclude spinal cord lesions or other neuropathies.
- **Management:**
  - **IV immunoglobulins (IVIG)**: First-line therapy, as effective as plasma exchange; fewer side effects.
  - **Plasma exchange**: Alternative to IVIG.
  - **Steroids**: Not beneficial.
  - **Respiratory Monitoring**:
    - Regular FVC assessment.
    - FVC < 1 L or < 15 mL/kg indicates mechanical ventilation need.
    - Rising $PaCO_2$ is an indicator for mechanical ventilation.
- **Prognosis:**
  - 20% of patients may have permanent disability; 5% mortality.

- **Poor prognostic factors**: Age > 40, poor upper limb strength, history of diarrheal illness (*Campylobacter jejuni*), high anti-GM1 antibody titres, need for ventilatory support.
- Contradictory evidence exists on whether gradual or rapid onset impacts prognosis.

Miller Fisher syndrome

- areflexia, ataxia, ophthalmoplegia
- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. **The eye muscles are typically affected first**
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- **anti-GQ1b antibodies are present in 90% of cases**

Radial nerve (C5-8)

Radial Nerve	Injury/Disorder	Cause	Clinical Features	Treatment
Radial Nerve Palsy	Wrist drop (Saturday night palsy)	Prolonged compression (e.g., during sleep, crutches), trauma	Wrist and finger extension weakness, inability to extend the wrist, decreased sensation on dorsum of hand	Splinting, physical therapy, NSAIDs, recovery in weeks to months, surgical intervention if persistent
Radial Tunnel Syndrome	Compression neuropathy	Compression of nerve in radial tunnel	Lateral elbow pain, similar to tennis elbow but more distal, weakness in wrist extension	Physical therapy, NSAIDs, activity modification, surgical decompression if severe
Posterior Interosseous Nerve Syndrome	Motor-only radial nerve palsy	Compression at the arcade of Frohse or trauma	Weakness in finger extension, forearm pain, no sensory loss	Rest, splinting, physical therapy, surgical decompression if needed
Humeral Shaft Fracture	Radial nerve injury due to fracture	Fracture of the midshaft of the humerus	Wrist drop, weakness in triceps if injury is proximal, sensory loss over the dorsum of the hand	Fracture management (casting/surgery), nerve monitoring, potential nerve repair

Radial Nerve	Injury/Disorder	Cause	Clinical Features	Treatment
Superficial Radial Nerve Entrapment	Wartenberg's syndrome	Compression at the wrist (e.g., tight watchbands, trauma)	Pain and paresthesia on the dorsum of the hand, no motor deficits	Avoidance of compression, splinting, NSAIDs, surgical release if necessary
Radial Nerve Neuritis	Inflammation of the nerve	Overuse, systemic inflammatory conditions (e.g., RA)	Pain, tingling, burning sensation in forearm or dorsum of hand	Anti-inflammatory drugs, corticosteroids, physiotherapy

Radial nerve neuropathy

Question	Answer
Radial nerve rout	C5-8
Typical injury	Fractured midshaft of humerus/compression of axilla by chair crutches. 'Saturday night palsy',
Motor loss?	extensor muscles (forearm, wrist, fingers, thumb)
Sensory loss?	▪ dorsal aspect of lateral 3 1/2 fingers ▪ anatomical snuffbox
The commonest site of sensory loss	anatomical snuffbox (a small area between the dorsal aspect of the 1st and 2nd metacarpals)
Sign?	wrist drop

Median nerve (C6-8, T1)

Median Nerve	Injury/Disorder	Cause	Clinical Features	Treatment
Carpal Tunnel Syndrome (CTS)	Compression neuropathy	Repetitive hand movements, wrist flexion, pregnancy, obesity	Numbness, tingling, or pain in the thumb, index, middle, and radial half of the ring finger; nighttime symptoms, weakness in thumb opposition	Wrist splinting (especially at night), NSAIDs, corticosteroid injections, surgical release for severe cases

Median Nerve	Injury/Disorder	Cause	Clinical Features	Treatment
Pronator Teres Syndrome	Compression at elbow	Repetitive forearm pronation and wrist flexion, trauma	Pain in the proximal forearm, sensory loss in the palm (unlike CTS), weakness in pronation, no nighttime symptoms	Activity modification, physical therapy, surgical decompression if conservative treatment fails
Anterior Interosseous Nerve Syndrome (AINS)	Motor-only neuropathy	Compression at the forearm, trauma	Weakness in thumb and index finger flexion (unable to make "OK" sign), no sensory loss	Rest, physical therapy, surgical intervention if persistent
Median Nerve Laceration	Direct nerve injury	Lacerations or deep cuts to the forearm or wrist	Loss of thumb opposition, weakened forearm pronation, sensory loss over the lateral palm and fingers	Surgical repair, nerve grafting, physical therapy for rehabilitation
Hand of Benediction	High median nerve injury	Proximal forearm injury (e.g., fractures, deep cuts)	Inability to flex the index and middle fingers when trying to make a fist, thumb weakness	Surgical repair, nerve grafting, splinting, and physical therapy
Median Nerve Neuritis	Inflammation of the nerve	Systemic conditions (e.g., diabetes, RA), overuse	Pain, tingling, burning sensation in the forearm or palm	Anti-inflammatory medications, corticosteroids, managing underlying conditions, physical therapy

Common questions about median nerve:

Question	Answer
Rout	C6-8, T1
Typical injury?	Fracture of supracondylar humerus/ Carpal tunnel syndrome
Motor deficit?	Opposition of thumb/Lateral finger flexion (**ulnar deviation of wrist**)/**wrist flexion** /(LOAF) muscles
Sensory deficit	Dorsal-palmar lateral 3.5 fingers/thenar eminence
Sign?	Ape hand (loss of Opponens pollicis)/Pope's hand (open digits 1-3 when trying to make fist)

Carpal tunnel syndrome

Aspect	Details
Definition	A condition caused by compression of the median nerve as it travels through the carpal tunnel in the wrist.
Nerve Roots	C5–T1
Common Causes	Repetitive hand movements, wrist trauma, rheumatoid arthritis, pregnancy, diabetes, hypothyroidism.
Clinical Features	Numbness, tingling, and pain in the thumb, index, middle, and radial half of the ring finger; weakness in the hand; night-time symptoms.
Motor Deficit	Weakness of the thenar muscles leading to difficulty with thumb opposition and abduction (affecting fine motor skills).
Sensory Deficit	Decreased sensation in the thumb, index, middle, and radial half of the ring finger; spared sensation on the palm due to palmar cutaneous branch.
Diagnostic Tests	Tinel's sign (tapping over the carpal tunnel), Phalen's test (holding the wrist in flexion for 30-60 seconds to elicit symptoms), nerve conduction studies.
Treatment	Conservative: wrist splinting, NSAIDs, corticosteroid injections. Surgical: carpal tunnel release if severe or unresponsive to conservative measures.

Pronator teres syndrome

Aspect	Details
Definition	A condition involving compression of the median nerve as it passes between the two heads of the pronator teres muscle in the forearm.
Nerve Roots	C6–T1
Common Causes	Repetitive pronation/supination movements, direct trauma, hypertrophy of the pronator teres muscle.
Clinical Features	Pain and tenderness in the proximal forearm, weakness in the forearm and hand, decreased grip strength, and numbness/tingling in the thumb, index, and middle fingers. Symptoms are often exacerbated by pronation.
Motor Deficit	Weakness of forearm pronation and finger flexion; potentially affects the flexor pollicis longus, flexor digitorum profundus (index and middle fingers), and flexor digitorum superficialis.
Sensory Deficit	Numbness or tingling in the palm and fingers innervated by the median nerve, sparing the palmar cutaneous branch (unlike carpal tunnel syndrome).
Diagnostic Tests	Pronator compression test (pain and reproduction of symptoms with pressure on the pronator teres), nerve conduction studies, EMG.
Differentiating Features	Unlike carpal tunnel syndrome, there is no worsening of symptoms at night and the palmar cutaneous branch is typically affected.
Treatment	Conservative: rest, activity modification, NSAIDs, splinting. Physical therapy may be beneficial. Surgical: decompression in cases resistant to conservative management.

Anterior interosseous syndrome

Aspect	Details
Definition	A neuropathy involving the anterior interosseous nerve, a branch of the median nerve, affecting forearm muscles.
Nerve Roots	C8–T1
Common Causes	Trauma, compression injuries (e.g., forearm fractures, tight casts), repetitive strain.
Motor Deficit	Weakness in thumb flexion (flexor pollicis longus), index finger flexion (flexor digitorum profundus), and pronation of the forearm (pronator quadratus).
Sensory Deficit	Typically none, as the anterior interosseous nerve is a motor branch only.
Clinical Features	Inability to form an "OK" sign due to weakness in thumb and index finger flexion.
Diagnosis	Physical exam (e.g., "OK" sign test), electromyography (EMG) for nerve assessment.
Treatment	Conservative management with rest, splinting, and physical therapy; surgical decompression if severe or persistent.

Ulnar nerve

Aspect	Details
Nerve Roots	C8–T1
Common Causes of Injury	- Compression at the elbow (cubital tunnel syndrome) - Fractures/dislocations of the elbow - Compression at the wrist (Guyon's canal syndrome) - Prolonged pressure on the palm or elbow
Motor Deficit	- Weakness in flexion of the fourth and fifth digits (e.g., flexor carpi ulnaris, flexor digitorum profundus to the ring and little fingers) - Loss of function in the intrinsic hand muscles (e.g., interossei, lumbricals to fourth and fifth digits, adductor pollicis) - Claw hand deformity (hyperextension at MCP joints and flexion at IP joints of the fourth and fifth digits)
Sensory Deficit	- Sensory loss on the palmar and dorsal surfaces of the medial one and a half fingers (ring and little fingers) and corresponding part of the hand
Clinical Features	- Claw hand - Weak grip strength, especially in actions involving fine motor control (e.g., writing, handling small objects) - Positive Froment's sign (weakness in adductor pollicis)
Common Tests	- **Tinel's sign** (at elbow or wrist): Tapping over the ulnar nerve at the elbow or wrist elicits tingling. - **Froment's sign:** Difficulty holding paper between thumb and index finger indicates weakness in adductor pollicis. - **EMG/Nerve conduction studies:** determine the injury site.
Treatment Options	- Conservative: Avoiding pressure, splinting, NSAIDs - Physical therapy - Surgical decompression or transposition if severe or refractory

Proximal and distal lesions of the ulnar nerve lead to claw hand deformity.

Common questions about ulnar nerve

Question	Answer
Rout ?	**C8-T1**
Typical injury?	Fracture of epicondyle of humerus
Motor deficit?	Medial finger flexion/wrist flexion
Sensory deficit?	Medial 1.5 fingers/hypothenar eminence
Sign?	Radial deviation of wrist upon flexion/**claw hand**

Commonly tested nerves of the lower limbs

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Femoral nerve	Knee extension, thigh flexion	Anterior and medial aspect of the thigh and lower leg	• Hip and pelvic fractures • Stab/gunshot wounds
Obturator nerve	**Thigh adduction**	Medial thigh	**Anterior hip dislocation**
Lateral cutaneous nerve of the thigh	None	Lateral and posterior surfaces of the thigh	Compression of the nerve near the ASIS → meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve
Tibial nerve	Foot plantarflexion and inversion	Sole of foot	▪ Not commonly injured as deep and well protected. ▪ Popliteal lacerations, posterior knee dislocation
Common peroneal nerve	Foot dorsiflexion and eversion Extensor hallucis longus	Dorsum of the foot and the lower lateral part of the leg	▪ Injury often occurs at the neck of the fibula Tightly applied lower limb plaster cast ▪ Injury causes foot drop
Superior gluteal nerve	Hip abduction	None	▪ Misplaced intramuscular injection ▪ Hip surgery ▪ Pelvic fracture ▪ Posterior hip dislocation ▪ **Injury results in a positive Trendelenburg sign**

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Inferior gluteal nerve	Hip extension and lateral rotation	None	▪ Generally injured in association with the sciatic nerve ▪ Injury results in difficulty rising from seated position. Can't jump, can't climb stairs

Sciatic nerve palsy

Nerve root →L4–S3 (Sciatic nerve splits into **tibial nerve** and **common peroneal nerve**)

Injuries of sciatic nerve branches

Aspect	Common Peroneal Nerve Injury	Tibial Nerve Injury
Nerve Root	L4–S2	L4–S3
Common Causes	- Fracture of the fibular head - Compression (e.g., tight casts, sitting cross-legged, lithotomy position during surgery)	- Trauma of the knee or leg (e.g., tibial fracture) - Baker cyst (proximal lesion) - Tarsal tunnel syndrome (distal lesion)
Motor Deficit	- Superficial peroneal nerve: paralysis of peroneus longus and brevis → impaired foot eversion - Deep peroneal nerve: paralysis of foot and toe dorsiflexors (e.g., tibialis anterior) → foot drop, steppage gait	- Paralysis of biceps femoris (long head) - Paralysis of foot flexors (e.g., triceps surae) → inability to stand on/curl toes or invert foot - Proximal lesions: eversion of the foot at rest
Sensory Deficit	- Superficial peroneal nerve: lateral surface of the lower leg, dorsum of feet/toes except the space between first and second toe - Deep peroneal nerve: area between the first and second toes (flip-flop zone)	- Sensory loss over the sole of the foot

The commonest cause of acute foot drop after prolonged bed rest is entrapment common peroneal neuropathy at the neck of fibula.

Diagnosis

- Usually, a clinical diagnosis
- Positive **Tinel sign**: radiating paresthesia triggered by tapping the flexor retinaculum posterior to the medial malleolus
- **Pain** upon foot dorsiflexion with eversion
- Diminished sensation on the plantar area of the foot
- Nerve conduction studies: slow conduction velocity in the medial and lateral plantar nerves

Treatment

- Initially conservative (Rest, NSAIDs, physiotherapy, use of orthotic shoes)
- Local injection of steroids into the tarsal canal (if no improvement)
- Surgical decompression

> **Tarsal tunnel syndrome**
> **entrapment of the posterior tibial nerve as it travels through the tarsal tunnel, this tunnel is found along the inner leg behind the medial malleolus → painful foot**

Sleep paralysis

Definition

- Sleep paralysis is a common condition characterised by transient paralysis of skeletal muscles, which occurs when awakening from sleep or less often while falling asleep.
- It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye movement) sleep.
- Mechanism is believed to involve a dysfunction in REM sleep.
- Males and females are affected equally.

Feature

- **aware but unable to move.**
- may include: hallucinations, fear.
- **A feeling of suffocation may be present** (although the respiratory muscles are only ever mildly affected in comparison with the limbs).
- Episodes generally last less than a couple of minutes.

Associations

- May occur in those who are otherwise healthy
- Narcolepsy
- Familial
- Can be triggered by sleep deprivation, psychological stress, or abnormal sleep cycles

Treatment

- Reassured that the condition is common and not serious.
- Other options that may be tried include sleep hygiene, cognitive behavioural therapy, and antidepressants.
- If troublesome, **clonazepam** may be used

Narcolepsy

Definition: **Daily periods of excessive daytime sleepiness for ≥ 3 months**

Pathophysiology

- **Narcolepsy type 1** (narcolepsy with cataplexy): autoimmune, structural lesion → loss of **lateral hypothalamic** neurons, which produce hypocretin-1 and hypocretin-2 (i.e. orexin A and orexin B) → hypocretin (orexin) deficiency → dysregulation of sleep-wake cycles
- **Narcolepsy type 2** (narcolepsy without cataplexy): Idiopathic (has normal CSF orexin-A levels)

Features: **Daytime sleepiness with cataplexy, hypnagogic hallucinations** (occur while going to sleep), **and sleep paralysis.**

Diagnosis: Clinical, supported by:

- **Overnight polysomnogram (to rule out other sleep disorders)**
- **Multi sleep latency test** (demonstrates an average sleep latency ≤8 minutes and/or at least two sleep-onset rapid eye movement periods)
- Lumbar puncture: decreased CSF hypocretin-1 (orexin A) levels

Treatment: **CNS stimulants (modafinil,** 200 mg as a single daily dose in the morning, are the treatment of choice).

Cataplexy

- **Sudden, transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened).**
- **Features range from buckling knees to collapse.**
- **Longer episodes can be associated with hallucinations.**
- **Around two-thirds of patients with narcolepsy have cataplexy.**

Altitude related disorders

There are three main types of altitude-related disorders: **occurs due to chronic hypobaric hypoxia, which develops at high altitudes**

Acute mountain sickness (AMS)	High altitude pulmonary oedema (HAPE)	High altitude cerebral edema (HACE)
▪ Occurs **above 2,500 - 3,000m** ▪ **Presented with** headache, nausea, fatigue ▪ **Prevented by** gaining altitude at no more than 500 m per day and acetazolamide (a carbonic anhydrase inhibitor) ▪ **Generally a self-limiting** condition and descent is the best treatment.	▪ Fatal condition occurs **above 4,000m** ▪ **Presents with** classical pulmonary oedema features ▪ **Managed by** descent, oxygen + reducing systolic pulmonary artery pressure (nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors)	▪ Fatal conditions occur **above 4,000m** ▪ **Presents with** headache, ataxia, papilloedema ▪ **Managed by** descent and dexamethasone

Selective serotonin reuptake inhibitors (SSRIs)

Drugs: Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram.

Indications

- Psychiatric disorders: Depression (1st -line), anxiety, anxiety, panic, psychosis)
- Premature ejaculation
- Irritable bowel syndrome

Side effects (SSRIs):

- **S**erotonin syndrome,
- **S**IADH → hyponatraemia
- **R**ocking (movement disorders),
- **I**nsomnia (stimulating effects), and
- **S**exual dysfunction.

Contraindications

- Concomitant use with other serotonergic drugs (e.g., MAOIs, linezolid, St. John's wort, dextromethorphan, meperidine, methylene blue and triptans)
- Paroxetine in pregnant patients (may cause fetal cardiovascular malformations in the first trimester and fetal pulmonary hypertension in the third trimester)

Discontinuation

- SSRIs should be gradually reduced over 4-week period (**this is not necessary with fluoxetine**).

Special cases

- Sertraline is safer than other antidepressants in **post myocardial infarction**
- NICE guidelines recommend avoiding SSRIs in patient taking anticoagulants (**warfarin / heparin**) and considering **mirtazapine**.
- Citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in combination with other QT-prolonging drugs.

Lithium toxicity

Lithium pharmacology

- **Mechanism of action:** unknown mechanism → mood stabilising
- **Clinical use:** mainly in bipolar disorder
- **Side effects:** **fine tremor**, secondary nephrogenic diabetes insipidus (polyuria, mild thirst), thyroid enlargement (hypothyroidism), hyperparathyroidism (**hypercalcaemia**) and weight gain.
- **Contraindications:** renal impairment, **first trimester of pregnancy (associated with Ebstein's anomaly) and during lactation.**
- Has a very narrow therapeutic range (0.4-1.0 mmol/L) and a Long plasma half-life (20 h). Excreted primarily by the kidneys.
- Monitoring
  - ⇨ Lithium blood level (taken 12 hours post-dose): every 3 months.
  - ⇨ Thyroid and renal function: before starting treatment and then every 6 months
- **Lithium toxicity** generally occurs with serum level > 1.5 mmol/L.

Precipitating factors of lithium toxicity

- **Dehydration**
- **Acute kidney injury**
- **Electrolyte imbalance**
- **Drugs:** diuretics (especially bendroflumethiazide), ACE inhibitors & **ARB**, NSAIDs, Metronidazole, Tetracycline, Phenytoin, Ciclosporin, Methyldopa.

Features

- **Acute or acute-on-chronic toxicity:** present with GI symptoms (nausea, vomiting, and diarrhea), neurologic symptoms develops later.
- **Chronic toxicity**: present with neurologic features (confusion or agitation, **ataxia, dysarthria, coarse tremor,** clonus, hyperreflexia, seizures, and coma).

Diagnosis

- History of lithium intake + GI or neurologic features + supratherapeutic lithium level
- **A single normal level does not rule out the diagnosis, and serial level should be performed.**

Management: Supportive

- **Initial:** check renal function and serum electrolytes. Correct electrolyte imbalance and fluid resuscitation. Mild-moderate toxicity may respond to volume resuscitation.
- **Lithium levels** should be taken but may be of limited value in the acute setting (rapid results may not be available; levels are not reliable in acute toxicity with sustained-release preparations, it correlate more closely with chronic toxicity.).
- **GI decontamination: whole bowel irrigation** in severe symptoms due to **sustained-release** preparations. **No rule for Activated charcoal as it does not bind to lithium.**
- **Indications for hemodialysis**
  - ⇨ Serum lithium level > 4 mEq/L and kidney dysfunction or > 5 mEq/L regardless of RFT
  - ⇨ Altered mental status (eg, confusion), seizures, or life-threatening dysrhythmias

> **Lithium slowly redistributes from the serum into the CNS. Therefore, in acute poisoning, GI symptoms predominate early, while in chronic poisoning, neurological symptoms predominate.**

> **Toxicity may be precipitated by dehydration, renal failure, diuretics (especially bendroflumethiazide) or ACE inhibitors and ARBs**

Lithium monitoring recommendation (NICE guidelines 2017)

RFT and TFT	Serum lithium levels	ECG
before treatment and every 6 months	1 week after starting treatment or dose change and then every 3 months	For people at high risk of cardiovascular disease

> **Sodium valproate is the second-line therapy for bipolar disorder in patients who do not tolerate lithium or where it's contraindicated.**

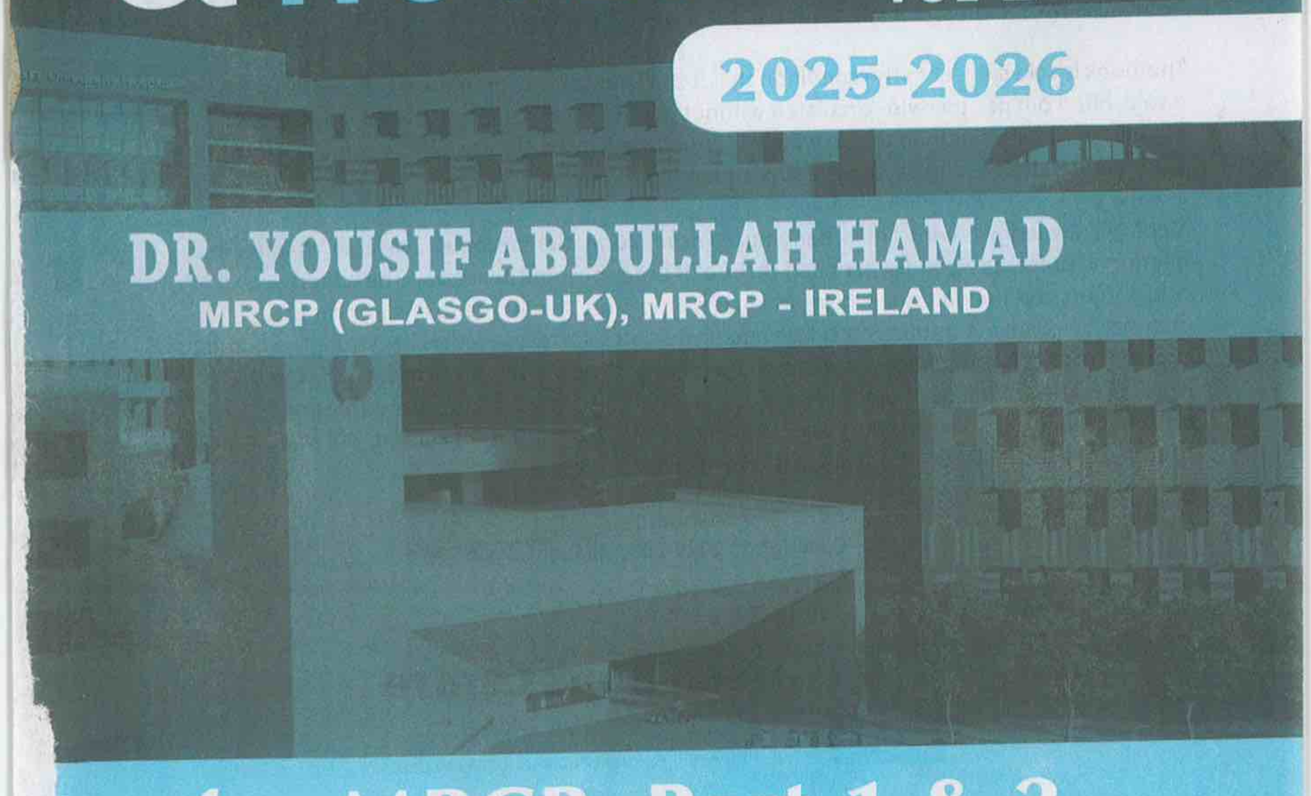
> **Tremors with lithium:**
> - **Fine tremor → side effect of therapeutic**
> - **Course tremor → sign of toxicity**

NOTES & NOTES

4TH Edition

VOL 2

2025-2026



DR. YOUSIF ABDULLAH HAMAD

MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

FBC

Fareed Book Centre

© Copyright 2025-2026

NOTES AND NOTES

4th Edition

DR. YOUSIF ABDULLAH HAMAD
MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the Copyright Holders.

This book is sold subject to the condition that it shall not, by way of trade or otherwise, be lent, resold, hired out or otherwise circulated without the publisher's prior consent in any form of binding or cover other than that in which it is published and without a similar condition including this condition being imposed on the subsequent purchaser.

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editors, contributors and the publishers have, as far as it is possible, taken care to ensure that the information given in this text is accurate and up-to-date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice. Neither the publisher nor the authors assume any responsibility for any loss or injury and/or damage to person or property arising out of or related to any use of the material contained in this handbook.

Copyright © 2025-2026 All Rights Reserved

Fareed Book Centre
Discover Something New
www.fareedbookcentre.com
156/8, MCB Road, Gulgasht Multan. | 03081401299

SOLE DISTRIBUTOR

Head Office 156/B (Fareed Book Centre) Gulgasht Colony Multan
03081401299
Info@fareedbookcentre.com

Shop No. 9 adjacent Bakhtawar Amir Medical & Dental College Multan
03168081199
Info@fareedbookcentre.com

V-2

CONTENT

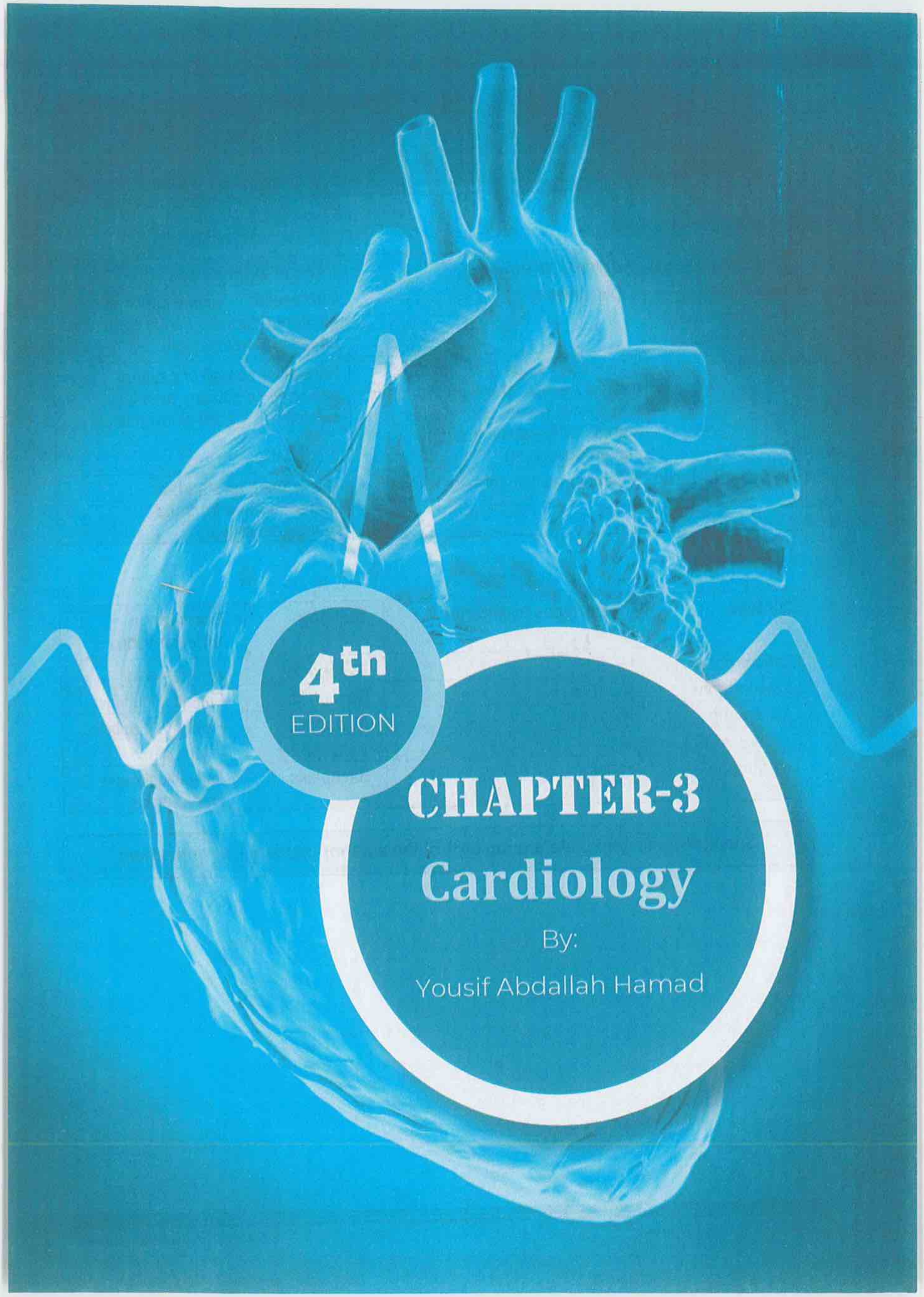
SL	Topic	Page
	Cardiology	1
1	Coronary Arteries	2
2	ECG	5
3	PR Interval	5
4	ST Depression	7
5	T Wave	8
6	Q Waves	8
7	ECG: St Elevation (STE)	10
8	ECG: Axis Deviation	12
9	Bundle Branch Block (BBB)	14
10	Bifascicular And Trifascicular Block	16
11	QT Interval	18
12	ECG: Junctional Escape Rhythm	19
13	ECG: U Wave	19
14	Vascular Lesions	20
15	Angina Pectoris	20
16	Acute Coronary Syndrome (ACS)	24
17	Myocardial Infarction (MI)	25
18	Subclavian Steal Syndrome	31
19	Peripheral Vascular Disease	32
20	Aortic Aneurysms	34
21	Aortic Dissection	36
22	Coarctation of The Aorta	39
23	Hypertension	41
24	Pulmonary Arterial Hypertension (PAH)	47
25	Mitral Stenosis (MS)	49
26	Mitral Regurgitation (MR)	50
27	Mitral Valve Prolapse (MVP)	50
28	Aortic Regurgitation (AR)	51
29	Aortic Stenosis (AS)	53
30	Heyde's Syndrome	55
31	Bicuspid Aortic Valve	55
32	Tricuspid Regurgitation	56
33	Syncope	57
34	Vertigo	59
35	Supraventricular Tachycardia (SVT)	63
36	Premature Ventricular Ectopic (PVES)	64
37	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	65
38	Atrial Fibrillation (AF)	66
39	Atrial Flutter	68
40	Multifocal Atrial Tachycardia (MAT)	69
41	Atrial Myxoma	70
42	Heart Block	71
43	Pacemakers	73
44	Pacemaker Syndrome	74
45	Brugada Syndrome	75
46	Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	77
47	Ventricular Tachycardia (VT)	78
48	Long QT Syndrome	79
49	Torsades De Pointes (TDP)	80
50	Wolff-Parkinson White (WPW)	81
51	Antiarrhythmics: Vaughan Williams Classification	83
52	Procainamide	84
53	Lidocaine	84
54	Atropine	85
55	Adenosine	86
56	Flecainide	87
57	Amiodarone	88

58	Thiazolidinediones (glitazones, insulin sensitizers)	87
59	Insulin	88
60	Diabetic ketoacidosis (DKA)	89
61	Hyperosmolar Hyperglycemic State (HHS)	90
62	Hypoglycaemia	91
63	Hypoglycemia Unawareness	92
64	Diabetic retinopathy	94
65	Diabetic neuropathy	95
66	Diabetic foot	97
67	Diabetic neuropathic arthropathy (Charcot's foot)	98
68	Necrobiosis lipoidica diabeticorum	99
69	Insulinoma	99
70	Glucagonoma	100
71	Maturity-onset diabetes of the young (MODY)	101
72	Latent autoimmune diabetes of adulthood (LADA)	102
73	Mitochondrial diabetes	102
74	Diabetes in pregnancy	103
75	Obesity	104
76	Familial Hyperlipidaemia	106
77	Secondary Hyperlipidemia	108
78	Lipid-lowering agents	110
79	Statins	111
80	Fibrates	114
81	Omega-3 Fatty Acids	114
82	Ezetimibe	114
83	Bempedoic Acid	115
84	PCSK9 Inhibitors	115
85	Inclisiran	116
86	Nicotinic acid (niacin)	116
87	Cholestyramine	117
88	Abetalipoproteinemia	117

89	Gynaecomastia	118
90	Physiological changes during pregnancy – endocrine	119
91	Physiological effects of LH, FSH, and sex hormones	120
92	Dihydrotestosterone (DHT)	121
93	Polycystic ovarian syndrome (PCOS)	125
94	Hypertrichosis	128
95	Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)	128
96	Amenorrhoea	129
97	Turner's syndrome	131
98	Premature ovarian failure	133
99	Menopause	134
100	Hormone replacement therapy (HRT)	135
101	Selective Estrogen Receptor Modulators (SERMs)	137
102	Androgen insensitivity syndrome	137
103	Disorders of sex hormones	138
104	Menstrual cycle	139
105	Delayed puberty	140
106	Gynaecomastia	141
107	Hypogonadism	142
108	Kallman's Syndrome vs Klinefelter's syndrome	146
109	Multiple endocrine neoplasia (MEN) (Autosomal dominant)	148
110	Multiple endocrine neoplasia	150
111	Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)	152

SL	Topic	Page
	Neurology	153
1	Transient ischaemic attack (TIA) and ischaemic stroke	154
2	Carotid artery stenosis	160
3	Specific stroke syndromes	162
4	Haemorrhagic stroke Spontaneous Intracerebral haemorrhage (ICH)	166
5	Subarachnoid haemorrhage (SAH)	168
6	Cerebral venous thrombosis (CVT)	171
7	Cervical vascular dissection	173
8	Localisation of a brain lesion	174
9	Cerebellar lesions	177
10	Localisation of speech problems	177
11	Pupil conditions	178
12	Visual field defects	184
13	Abnormal gait	186
14	Nystagmus	187
15	Chorea and Hemiballism	189
16	Cranial nerves	191
17	Optic nerve palsy	193
18	Oculomotor (third nerve) palsy	194
19	Posterior communicating artery aneurysm (PCA)	195
20	Trigeminal neuralgia	197
21	Abducens (VIth) nerve palsy	198
22	Facial (VII) nerve	199
23	Acoustic Neuroma (Vestibular Schwannoma)	202
24	Labyrinthine Infarction vs Viral Labyrinthine Dysfunction	203
25	Ptosis, Miosis and Mydriasis	204
26	Horner's syndrome	205
27	Bulbar and Pseudobulbar palsy	207
28	Epilepsy	208
29	Tourette Syndrome	212
30	Huntington's disease (HD)	212
31	Parkinsonism	214
32	Parkinson's disease (PD)	214
33	Anti-Parkinson drugs	217
34	Serotonin syndrome and Neuroleptic malignant syndrome (NMS)	219
35	Anticholinergic syndrome (overdose)	219
36	Dystonia	221
37	Botulism	222
38	Parkinson Plus syndromes	222
39	Normal pressure hydrocephalus (NPH)	224
40	Dementia	225
41	Delirium (Acute Confusional State)	228
42	Creutzfeldt-Jakob disease (CJD)	229
43	Transient global amnesia	230
44	Restless legs syndrome (RLS)	231
45	Essential tremor	232
46	Holmes tremor	233
47	Friedreich's Ataxia and Ataxic Telangiectasia	234
48	Motor neuron disease (MND)	236
49	Headache	238
50	Triptans	241
51	Idiopathic intracranial hypertension(IIH)	242
52	Multiple sclerosis (MS)	243
53	Myasthenia gravis (MG)	248
54	Lambert-Eaton myasthenic syndrome (LEMS)	250
55	Neurofibromatosis (NF)	251
56	Tuberous sclerosis (TS)	252
57	Brain Tumors	254
58	Von Hippel-Lindau syndrome (VHL)	255
59	Wernicke's encephalopathy	256
60	Korsakoff syndrome	257
61	Anti-NMDA receptor encephalitis	258
62	Lower back pain	259
63	Transverse Myelitis (TM)	260
64	Metastatic spinal cord compression	261

176	Gastroparesis	263
177	Gastric Cancer	265
178	Gastric Malt Lymphoma	267
179	Gastrointestinal Stromal Tumour (Gist)	268
180	Dyspepsia	269
181	Malabsorption	270
182	Jejunal Villous Atrophy	272
183	Coeliac Disease	273
184	Whipple's Disease	276
185	Tropical Sprue	277
186	Irritable Bowel Syndrome (IBS)	277
187	Lactose Intolerance	279
188	Melanosis Coli	280
189	Protein-Losing Enteropathy	280
190	Refeeding Syndrome	281
191	Mesenteric Ischaemia	282
192	Small Bowel Bacterial Overgrowth Syndrome	284
193	Spontaneous Bacterial Peritonitis (SBP)	285
194	Acute Pancreatitis	286
195	Chronic Pancreatitis	287
196	Pancreatic Cancer	289
197	Ascending Cholangitis	291
198	Gallstones (Cholelithiasis)	292
199	Bile-Acid Malabsorption	294
200	Primary Biliary Cirrhosis	295
201	Primary Sclerosing Cholangitis (PSC)	297
202	Cholangiocarcinoma	298
203	Liver Function Test	300
204	Acute Liver Failure (ALF)	303
205	Ascites	305
206	Liver Cirrhosis	307
207	Portal Hypertension	309
208	Hepatic Encephalopathy	310
209	Hepatorenal Syndrome (HRS)	311
210	Wilson's Disease	312
211	Alcohol Use Disorder	313
212	Non-Alcoholic Fatty Liver Disease (NAFLD) (Non-Alcoholic Steatohepatitis (NASH)	315
213	Drug-Induced Liver Disease	317
214	Budd-Chiari Syndrome	317
215	Hyperbilirubinemia And Jaundice	318
216	Autoimmune Hepatitis	320
217	Pregnancy-Associated Liver Disease	321
218	Haemochromatosis	322
219	Hepatocellular Carcinoma (HCC)	323
220	Hepatitis A (HAV)	325
221	Hepatitis B	325
222	Hepatitis C	328
223	Hepatitis D And E	329
224	Colorectal Cancer (CRC)	330
225	Peutz-Jeghers Syndrome (PJS)	333
226	Carcinoid Tumours	334
227	Carcinoid Syndrome	335
228	Diverticular Disease	336
229	Angiodysplasia	336
230	Inflammatory Bowel Disease (IBD) Crohn's Disease	338
231	Ulcerative Colitis	339
232	Microscopic Colitis	341
233	Toxic Megacolon (Toxic Dilatation of The Colon)	342
234	Diarrhoea	344
235	Gastrointestinal Parasitic Infections	347
236	Pseudomembranous Colitis (Clostridium Difficile)	348
237	Antibiotic Treatment for Clostridium Difficile (NICE Guideline/July 2021)	349
238	Hiccup	349



4th EDITION

CHAPTER-3

Cardiology

By:

Yousif Abdallah Hamad

Pituitary disorders

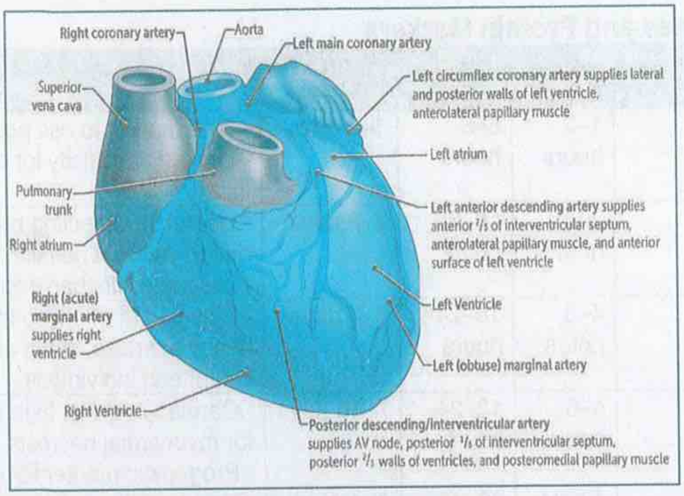
Pituitary gland anatomy and its clinical significance

Location	Adjacent structure	Clinical significance
Superiorly (5–10 mm above diaphragm sella)	Optic chiasm	Suprasellar extension of pituitary adenoma can lead to bitemporal hemianopia
Laterally	Cavernous sinus (3rd, 4th, 6th cranial nerves, maxillary branch of 5th cranial nerve, and internal carotid artery pass through cavernous sinus)	Parasellar spread of pituitary adenoma or pituitary apoplexy can lead to cranial nerve palsies
Antero-inferiorly	Posterior wall of sphenoid sinus	This is used as standard approach route for trans-sphenoidal surgery

Cell populations of the anterior pituitary gland

Cell type	% of cell types in anterior pituitary	Staining	Location in anterior lobe
Corticotrophs	15–20%	Basophilic	Anteromedial
Gonadotrophs	10–15%	Basophilic	Spread throughout
Lactotrophs	10–25%	Acidophilic	Randomly distributed
Somatotrophs	**50%**	**Acidophilic**	**Lateral part**
Thyrotrophs	<10%	Basophilic	Anteromedial and anterolateral

Somatotrophs constitute around 50% of the anterior pituitary cell population



Normal Pacing of the Heart (Conducting System)

Aspect	Details
Primary Pacemaker	- **Sinoatrial Node (SA Node):** Located in the right atrium, initiates electrical impulses at a rate of 60–100 bpm.
Conduction Pathway	1. **SA Node** → Generates the impulse. 2. **Atrial conduction pathways** → Spread through atria causing atrial contraction (P wave).
Secondary Pacemaker	- **Atrioventricular Node (AV Node):** Delays conduction to ventricles (0.1 second) to allow ventricular filling. Rate: 40–60 bpm.
Bundle of His	- Conducts impulses from AV node to the interventricular septum.
Purkinje Fibres	- Conduct impulses rapidly through ventricles, causing coordinated ventricular contraction. Rate: 20–40 bpm.
Backup Pacemakers	- If the SA node fails, the AV node takes over. - If both SA and AV nodes fail, Purkinje fibres act as pacemakers but at a slower rate.
ECG Correlation	- **P wave:** Atrial depolarisation (SA node). - **PR interval:** AV node conduction delay. - **QRS complex:** Ventricular depolarisation.

SA Node and AV Node

Aspect	Sinoatrial Node (SA Node)	Atrioventricular Node (AV Node)
Definition	- Primary pacemaker of the heart.	- Secondary pacemaker, relays electrical impulses from the atria to the ventricles.
Location	- Located at the junction of the superior vena cava and right atrium.	- Situated in the interatrial septum near the opening of the coronary sinus.
Blood Supply	- Supplied by the **RCA** in 60% of individuals and by the **LCx** in 40%.	- Supplied by the **RCA** in 85–90% and by the **LCx** in 10–15%.
Function	- Generates spontaneous electrical impulses (60–100 bpm) to initiate the cardiac cycle.	- Delays conduction (0.1 second) to allow ventricular filling. - Sets the pace if the SA node fails (40–60 bpm).

Cardiac Enzymes and Protein Markers

Marker	Rise Time	Peak Time	Return to Normal	Key Features
Myoglobin	1–2 hours	6–8 hours	1–2 days	- First marker to rise post-MI. - Limited specificity for cardiac injury.
CK-MB	2–6 hours	16–20 hours	2–3 days	- Useful for detecting **reinfarction** due to its short half-life. - Less specific than troponins.
CK (Total)	4–8 hours	16–24 hours	3–4 days	- Elevated in MI, hypothyroidism, heavy exercise, statin use, and Afro-Caribbean individuals.
Troponin T	4–6 hours	12–24 hours	7–10 days	- Cardiac-specific, high sensitivity for myocardial necrosis. - Prognostic marker for ACS.
AST	12–24 hours	36–48 hours	3–4 days	- Non-specific; not commonly used for MI diagnosis.
LDH	24–48 hours	72 hours	8–10 days	- Elevated in late stages of myocardial injury but lacks specificity.
GPBB (Glycogen Phosphorylase BB)	1–3 hours	Early marker	Short-lived	- Rises earlier than myoglobin, useful for detecting early cardiac injury.

Troponin Details

- **Types:**
  - Troponin C: Binds calcium to initiate actin-myosin interaction.
  - Troponin T: Binds tropomyosin.
  - Troponin I: Inhibits actin-myosin interaction.
- **Significance:**
  - Highly sensitive and specific for myocardial necrosis.
  - Degree of elevation correlates with infarct size and prognosis.
- **Non-MI Elevations:**
  - Pulmonary embolism, pulmonary hypertension.
  - Hypertension/hypotension with arrhythmias.
  - Myocarditis, sepsis, trauma, infiltrative disorders (e.g., sarcoidosis).
  - Drugs (e.g., Adriamycin, Herceptin, 5-FU).

CK-MB

- **Clinical Use:**
  - Historically used for ACS diagnosis but replaced by troponins.
  - Helpful for detecting reinfarction due to its short half-life.

Key Exam Points

- **Myoglobin:** First marker to rise.
- **CK-MB:** Best for reinfarction detection as it normalises quickly.
- **Troponins:** Stay elevated for up to 10 days and are the gold standard for ACS diagnosis.

ECG

PR interval

Definition

- The **PR interval** represents the time taken for the electrical impulse to travel from the **sinoatrial (SA) node** through the **atria**, **atrioventricular (AV) node**, and into the **ventricles**.

Normal PR Interval

- Duration: **0.12–0.20 seconds** (3–5 small boxes).
- Measured from the **beginning of the P wave** to the **start of the QRS complex**.

Abnormal PR Interval

Abnormality	Description	Possible Causes
Prolonged PR Interval (First-degree AV block)	PR interval >0.20 seconds.	Aging, AV nodal disease, medications (e.g., beta-blockers, calcium channel blockers), myocarditis, ischemia.
Shortened PR Interval	PR interval <0.12 seconds.	Pre-excitation syndromes (e.g., Wolff-Parkinson-White), Lown-Ganong-Levine syndrome.
Variable PR Interval	PR interval length fluctuates.	Second-degree AV block, complete heart block, or atrial fibrillation.

Clinical Relevance

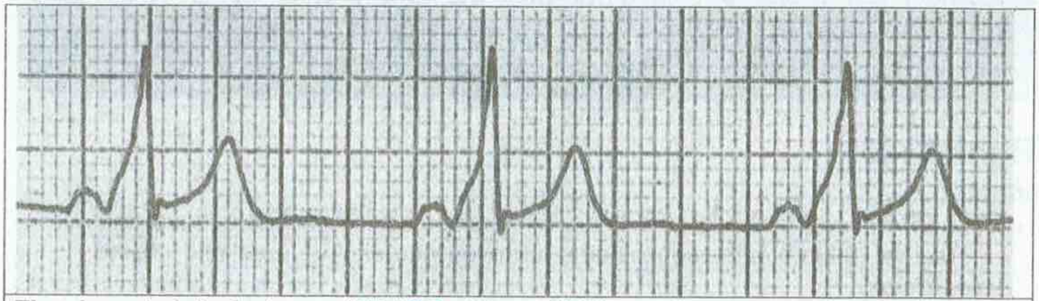
1. **Prolonged PR Interval (First-Degree AV Block)**:
   - Impulse conduction through the AV node is delayed.
   - Usually asymptomatic but may indicate underlying heart disease or be drug-induced.
2. **Shortened PR Interval**:
   - Associated with pre-excitation syndromes like **Wolff-Parkinson-White (WPW)**.
   - Can predispose to **tachyarrhythmias**.
3. **Variable PR Interval**:
   - Seen in **second-degree AV block** or **complete AV block**.
   - May require pacemaker implantation if symptomatic.

Conditions Associated with Abnormal PR Intervals

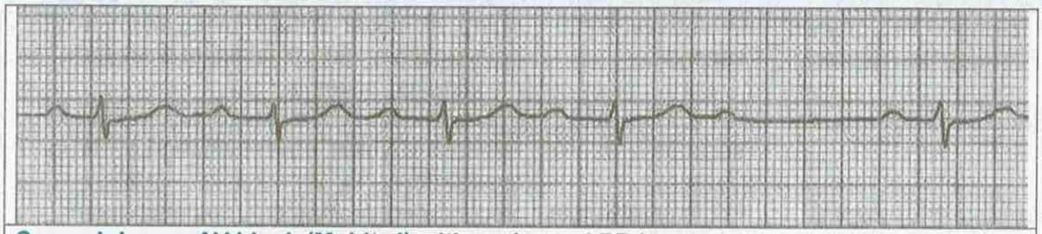
- **First-Degree AV Block**: PR interval consistently >0.20 sec.
- **Second-Degree AV Block** (Mobitz Type I and II): Progressive or sudden PR interval changes.
- **Third-Degree AV Block**: Complete dissociation between atrial and ventricular conduction.
- **Wolff-Parkinson-White Syndrome**: Short PR interval with a **delta wave** (slurred QRS upstroke).

Management

- **First-degree block**: No treatment if asymptomatic.
- **Second-degree/complete AV block**: May require **pacemaker** if symptomatic.
- **WPW Syndrome**: Ablation of the accessory pathway may be necessary to prevent tachyarrhythmias.

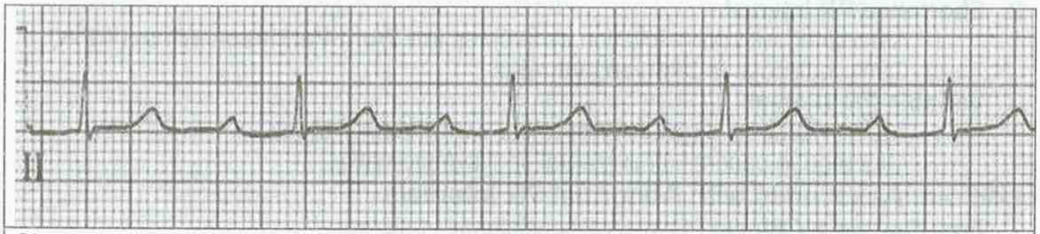


The characteristic features of Wolff-Parkinson-White syndrome are a short PR interval (<120ms), broad QRS and a slurred upstroke to the QRS complex, the delta wave.



Second degree AV block (Mobitz I) with prolonged PR interval

- the baseline PR interval is prolonged, and then further prolongs with each successive beat, until a QRS complex is dropped.
- The PR interval before the dropped beat is the longest (340ms), while the PR interval after the dropped beat is the shortest (280ms).



Sinus rhythm with marked 1st degree heart block (PR interval 340ms)

ST depression

Definition

- **ST depression** refers to the downward displacement of the ST segment below the baseline, indicating subendocardial ischemia or other cardiac abnormalities.

Types of ST Depression

1. **Horizontal ST Depression**:
   - Often indicates **myocardial ischemia**.
   - Seen in conditions like **unstable angina** or **non-ST elevation myocardial infarction (NSTEMI)**.
2. **Downsloping ST Depression**:
   - A more concerning sign of **severe ischemia**.
   - Associated with high-risk acute coronary syndromes (ACS).
3. **Upsloping ST Depression**:
   - Less specific for ischemia.
   - Can be a normal finding, especially during exercise stress tests.

Common Causes of ST Depression

Cause	Description
Myocardial Ischemia	Subendocardial ischemia due to reduced coronary perfusion.
NSTEMI	ST depression appears in leads corresponding to affected myocardial regions.
Unstable Angina	Presents with ST depression and T wave changes without myocardial necrosis.
Electrolyte Imbalance	Hypokalemia or hypomagnesemia can cause ST depression.
Left Ventricular Hypertrophy (LVH)	Secondary to strain patterns in ventricular overload.
Digoxin Effect	"Scooped" or downsloping ST depression characteristic of digoxin therapy.
Bundle Branch Block (BBB)	ST depression may appear in leads opposite to the block.
CNS Events (e.g., stroke)	Can cause generalized T wave and ST changes.

Diagnostic Value

- **ST depression** localized to specific leads can indicate the site of ischemia.
  - **Inferior Leads** (II, III, aVF): Inferior ischemia.
  - **Anterior Leads** (V1–V4): Anterior wall ischemia.
- In **exercise stress tests**, ST depression indicates **inducible ischemia** when present during physical exertion.

Management

- **Acute Ischemia or NSTEMI**:
  - Immediate medical therapy (antiplatelet agents, beta-blockers, nitrates, and anticoagulants).
  - Consider **angiography** or **PCI** based on clinical risk.
- **Digoxin Effect**: Adjust or discontinue digoxin if appropriate.
- **Electrolyte Imbalance**: Correct electrolyte disturbances (e.g., potassium or magnesium).
- **LVH or Strain Patterns**: Manage underlying hypertension or cardiac overload.

T wave

Definition

- The **T wave** reflects **ventricular repolarization** on the ECG. It corresponds to the recovery phase of the ventricles after contraction.

Normal T Wave Characteristics

- **Upright** in most leads except **aVR** and **V1**.
- Asymmetrical with a **gradual rise** and a **steeper decline**.
- **Amplitude**:
  - Less than **10 mm** in precordial leads.
  - Less than **5 mm** in limb leads.

Abnormal T Waves and Their Significance

Abnormality	Description	Causes
T Wave Inversion	Reversal of normal upright T wave.	Myocardial ischemia, infarction, myocarditis, bundle branch block, or CNS events.
Hyperacute T Waves	Broad, peaked T waves occurring early in myocardial infarction.	Early **STEMI**, hyperkalemia.
Flattened T Waves	Diminished amplitude of T wave.	Non-specific finding, **hypokalemia**, ischemia, or pericarditis.
Peaked T Waves	Tall, narrow, and symmetrical T waves.	**Hyperkalemia** (most commonly).
Biphasic T Waves	T wave with two phases (up then down or vice versa).	**Ischemia** or **hypokalemia**.
Camel-hump T Waves	Double peak in the T wave.	Hypothermia, CNS events, or electrolyte imbalance.

Q waves

Definition

- **Q waves** represent **initial depolarization of the interventricular septum** and may indicate myocardial injury or infarction when they become pathological.

Normal Q Waves

- **Small Q waves** are typically present in the left-sided leads (**I, aVL, V5, V6**).
- Duration: **<0.04 seconds (1 small box)**.
- Amplitude: Less than **25% of the R-wave** in the same lead.
- Physiological Q waves do not indicate myocardial damage.

Pathological Q Waves

- Indicate **prior myocardial infarction** due to **myocardial necrosis**.
- Criteria:
  - **Duration ≥0.04 seconds.**
  - Amplitude **≥25% of the R wave** in the same lead.
  - Found in **at least two contiguous leads** (e.g., leads I and aVL or V1 and V2).

Localization of Infarction by Q Waves

- **Inferior MI**: Q waves in **leads II, III, aVF**.
- **Anterior MI**: Q waves in **V1-V4**.
- **Lateral MI**: Q waves in **I, aVL, V5-V6**.
- **Posterior MI**: Often diagnosed indirectly via **tall R waves** in V1-V2 (mirror image).

Clinical Significance

- **Pathological Q waves** suggest **old infarction** or **irreversible myocardial damage**.
- May develop within **hours to days** of an acute myocardial infarction (MI).
- Presence does not necessarily correlate with current myocardial ischemia.
- **Persistent Q waves** indicate **scar tissue** from previous MI.

Differential Diagnosis of Pathological Q Waves

- **Myocardial infarction** (most common).
- **Cardiomyopathy** (e.g., hypertrophic cardiomyopathy).
- **Myocarditis.**
- **Wolff-Parkinson-White syndrome** (pseudo-infarct pattern).
- **Pulmonary embolism** (rarely).

Comparison of Differential Diagnoses of Pathological Q Waves

Condition	Description	ECG Features	Additional Clinical Features	Management Focus
Myocardial Infarction (MI)	Irreversible necrosis due to coronary artery occlusion.	Pathological Q waves in infarcted regions (≥0.04s, ≥25% R wave).	Chest pain, dyspnea, elevated cardiac biomarkers.	Reperfusion therapy (PCI, thrombolysis) and secondary prevention.
Hypertrophic Cardiomyopathy (HCM)	Thickened ventricular wall leading to abnormal septal depolarization.	Deep Q waves in **inferior** and **lateral leads** (I, aVL, V5, V6).	Syncope, dyspnea, sudden cardiac death risk, systolic murmur.	Beta-blockers, calcium channel blockers, or surgical myectomy.
Myocarditis	Inflammation of heart muscle, often viral.	Diffuse Q waves with non-specific ST-T changes.	Fever, fatigue, heart failure, arrhythmias.	Supportive care; treat infections if present.
Wolff-Parkinson-White (WPW)	Pre-excitation syndrome due to accessory pathway.	Q waves mimicking infarct pattern, **delta waves**, short PR interval.	Palpitations, syncope, risk of sudden cardiac death.	Antiarrhythmics or ablation therapy.
Pulmonary Embolism (PE)	Clot in pulmonary arteries causing right heart strain.	Q waves may appear in **III** with S waves in I (S1Q3T3 pattern).	Dyspnea, tachycardia, pleuritic chest pain.	Anticoagulation or thrombolysis.
Infiltrative Cardiomyopathies (e.g., Amyloidosis)	Deposition of abnormal proteins in myocardial tissue.	Small Q waves in **inferior** and **lateral leads**.	Heart failure symptoms, low voltage on ECG.	Treat underlying disease; symptomatic management.

ECG: ST elevation (STE)

Definition

- **ST-elevation** (STE) on ECG indicates **acute myocardial injury**, often due to **complete coronary artery occlusion.** It is a hallmark finding in **ST-Elevation Myocardial Infarction (STEMI).**

Criteria for STE Diagnosis

1. **≥ 1 mm elevation** in at least two adjacent limb leads (e.g., I, II, III, aVL, aVF).
2. **≥ 2 mm elevation** in two or more adjacent chest leads (e.g., V1–V6).
3. **New left bundle branch block (LBBB)** can also indicate STEMI if accompanied by clinical symptoms of ischemia.

Causes of ST Elevation

1. **Acute Myocardial Infarction (STEMI)**: Most common cause, requires urgent reperfusion.
2. **Pericarditis**: Diffuse ST elevation across multiple leads without reciprocal ST depression.
3. **Early Repolarization**: A benign pattern often seen in young, healthy individuals.
4. **Left Ventricular Aneurysm**: Persistent STE after a myocardial infarction.
5. **Prinzmetal's Angina (Vasospasm)**: Transient ST elevation due to coronary vasospasm.

Differentiating STE Causes on ECG

- **STEMI**: Localized elevation with reciprocal ST depression in opposing leads.
- **Pericarditis**: Diffuse STE without reciprocal changes; associated with PR segment depression.
- **Early Repolarization**: Concave-upward STE with notched J-points.
- **LV Aneurysm**: STE persists weeks to months after infarction, often in the same leads as the prior MI.

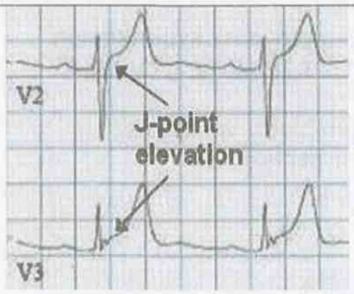
Management Based on STE

- **STEMI**: Requires **urgent reperfusion therapy** via **primary PCI** or **thrombolysis** if PCI is not available within 120 minutes.
- **Pericarditis**: Managed with **NSAIDs** and **colchicine.**
- **Vasospastic Angina (Prinzmetal's Angina)**: Treated with **calcium channel blockers** and nitrates.

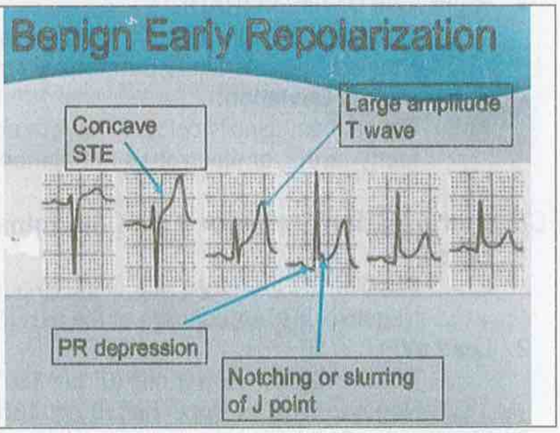
Comparison of Causes of ST Elevation (STE)

Cause	Description	ECG Pattern	Additional Features	Management
STEMI	Complete coronary artery occlusion leading to myocardial necrosis.	Localized STE with **reciprocal ST depression** in opposing leads.	Symptoms: Severe chest pain, sweating, nausea.	**Urgent PCI** or **thrombolysis** if PCI unavailable.
Pericarditis	Inflammation of the pericardium, often viral or idiopathic.	Diffuse STE across multiple leads with **PR segment depression.**	Chest pain that worsens with lying down and improves on sitting up.	**NSAIDs** and **colchicine.**

Cause	Description	ECG Pattern	Additional Features	Management
Early Repolarization	Benign ECG variant often seen in young, healthy individuals.	Concave-upward STE, typically in precordial leads (V2-V5), with notched J-points.	No symptoms; more common in males and athletes.	No treatment needed.
Left Ventricular Aneurysm	Persistent wall motion abnormality post-MI, causing chronic STE.	Persistent STE in the same leads weeks after MI.	History of previous MI, risk of thrombus formation.	**Anticoagulation** to prevent embolism.
Prinzmetal's Angina (Vasospasm)	Coronary artery vasospasm causing transient ischemia.	Transient localized STE that resolves with vasodilation.	Occurs at rest, often at night; unrelated to exertion.	**Calcium channel blockers** (e.g., nifedipine).
Hyperkalemia	High potassium levels affecting myocardial depolarization.	STE with **peaked T waves** and wide QRS complexes.	Associated with muscle weakness, bradyarrhythmias.	**Calcium gluconate, insulin with glucose.**
Myocarditis	Inflammation of the heart muscle, often viral in origin.	STE with non-specific changes, including T wave inversion.	Symptoms: Fever, fatigue, heart failure.	Supportive care; treat underlying cause.



Early repolarization



ECG: axis deviation

Definition

The electrical axis on an ECG reflects the direction of the heart's electrical impulse. It helps identify abnormalities in cardiac conduction or structural heart disease.

Types of Axis Deviations

Type	ECG Lead Patterns	Causes
Normal Axis	Positive QRS in leads I and aVF	Normal heart function
Left Axis Deviation (LAD)	Positive QRS in lead I and negative QRS in aVF	- Left anterior fascicular block - Inferior MI - Left ventricular hypertrophy (LVH) - WPW syndrome
Right Axis Deviation (RAD)	Negative QRS in lead I and positive QRS in aVF	- Right ventricular hypertrophy (RVH) - Pulmonary embolism - Chronic lung disease - WPW syndrome
Extreme Axis Deviation (Northwest Axis)	Negative QRS in both leads I and aVF	- Ventricular tachycardia - Hyperkalemia - Severe ventricular enlargement

Clinical Significance

- **Left Axis Deviation (LAD):**
  - Associated with left-sided heart conditions such as **left ventricular hypertrophy** or **left anterior fascicular block**.
  - Can indicate **prior inferior myocardial infarction**.
- **Right Axis Deviation (RAD):**
  - Often seen in **right ventricular hypertrophy** or **pulmonary hypertension**.
  - May also indicate **acute pulmonary embolism** or **chronic lung disease**.
- **Extreme Axis Deviation:**
  - Uncommon; usually points to **severe conduction block, ventricular tachycardia**, or **electrolyte imbalances** (e.g., hyperkalemia).

ECG Interpretation Steps for Axis Determination

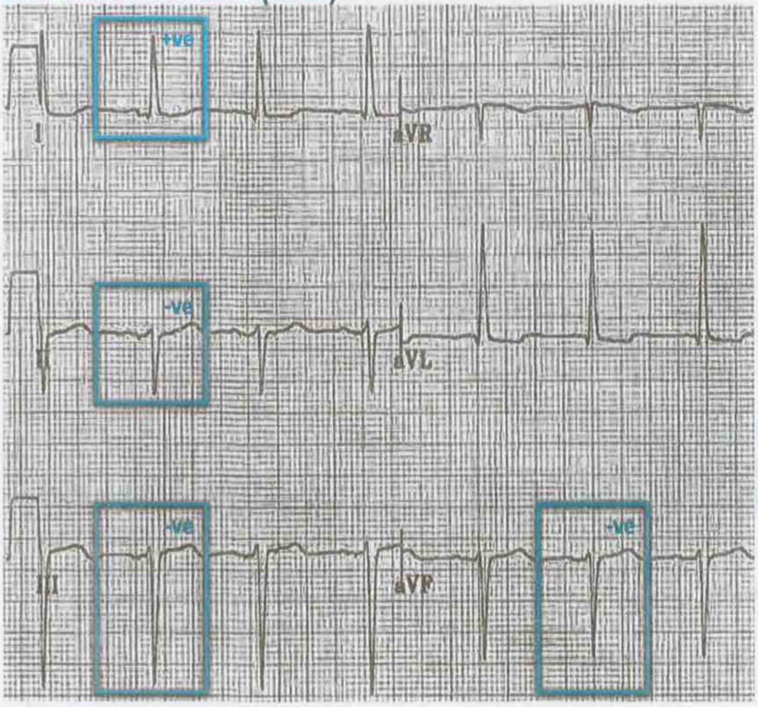
1. **Lead I:**
   - Positive QRS → Right side of the axis (0° to +180°).
   - Negative QRS → Left side of the axis (0° to -180°).
2. **Lead aVF:**
   - Positive QRS → Lower half (0° to +180°).
   - Negative QRS → Upper half (0° to -180°).
3. **Identify the Quadrant:**
   - Both leads positive: Normal axis.
   - Lead I positive, aVF negative: LAD.

- Lead I negative, aVF positive: RAD.
- Both leads negative: Extreme axis deviation.

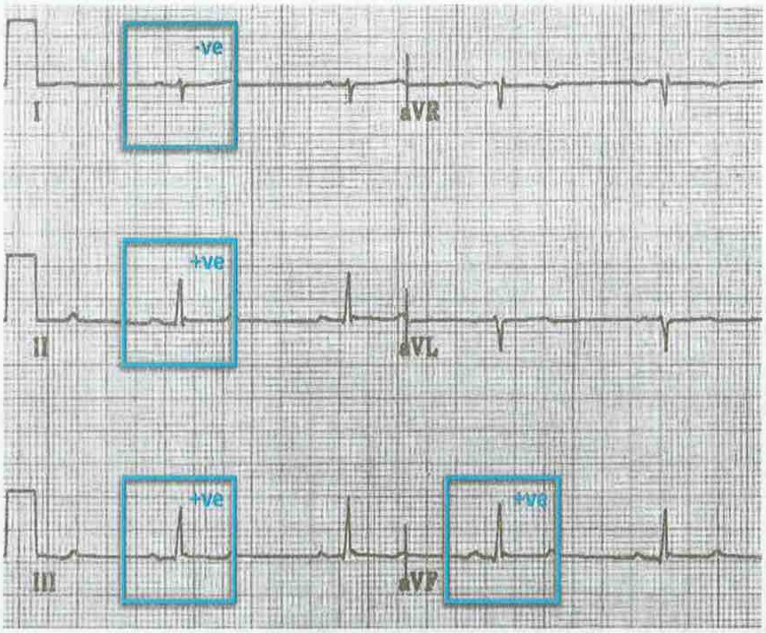
Management

- **Normal Axis**: No action needed.
- **LAD/RAD**: Investigate underlying conditions (e.g., LVH, RVH, MI).
- **Extreme Axis Deviation**: Urgent assessment for severe conduction issues or electrolyte abnormalities.

Left axis deviation (LAD)



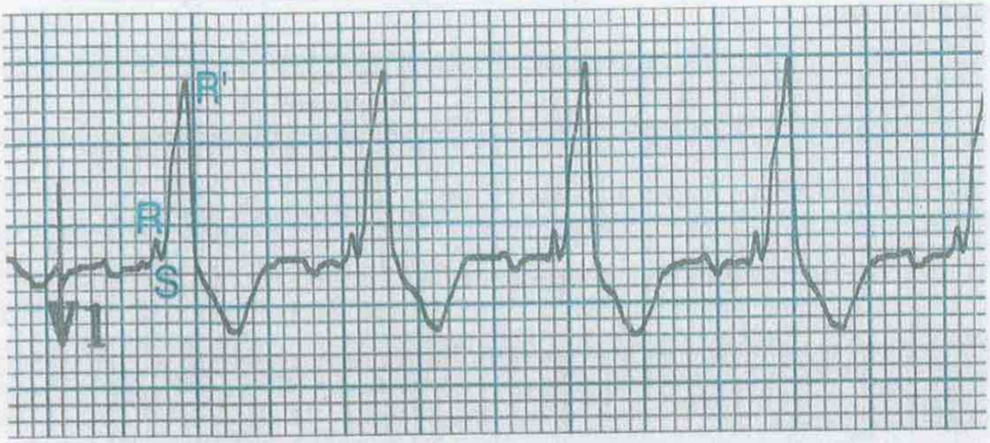
Right axis deviation (RAD)



Bundle branch block (BBB)

Types of Bundle Branch Block

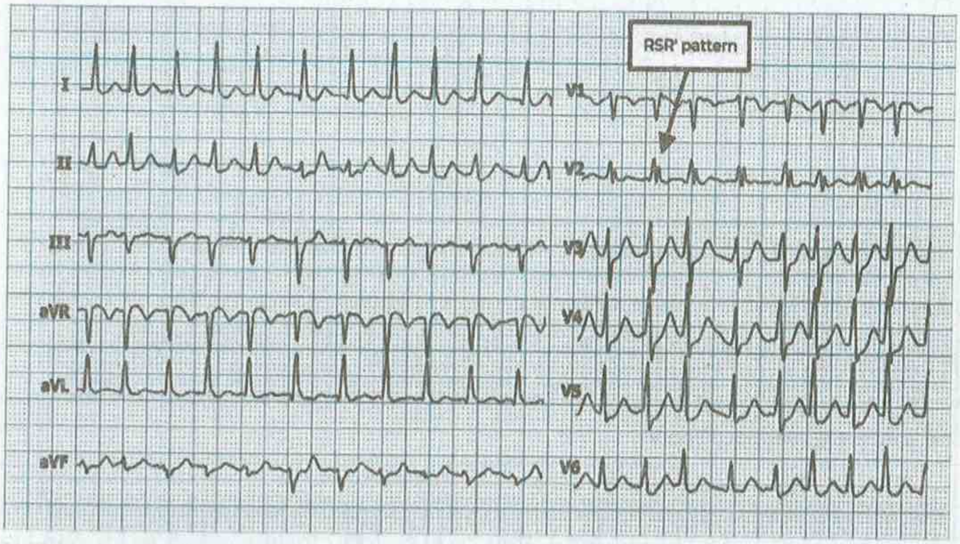
Type	ECG Criteria	Causes	Clinical Significance
Right Bundle Branch Block (RBBB)	- Wide QRS ≥ 120 ms - rSR' pattern in **V1-V3** - Wide, slurred **S wave** in lead I, aVL, V6	- Right ventricular hypertrophy (RVH) - Pulmonary embolism - Congenital heart disease (e.g., atrial septal defect)	May indicate right-sided heart strain or pulmonary disease but is sometimes seen in healthy individuals.
Left Bundle Branch Block (LBBB)	- Wide QRS ≥ 120 ms - Dominant **S wave** in V1 - Broad, notched R wave in leads I, aVL, V6 - Absence of Q waves in leads I, V5, and V6	- Left ventricular hypertrophy (LVH) - Ischemic heart disease (e.g., myocardial infarction) - Cardiomyopathy - Aortic stenosis	Often suggests underlying cardiac disease and may obscure signs of myocardial infarction on ECG.
Incomplete Bundle Branch Block	- QRS between 110-119 ms - Features of either RBBB or LBBB	- Can be seen in normal individuals or progress to complete BBB	Less severe conduction delay compared to complete BBB



Typical RSR' pattern ('M'-shaped QRS) in V1

Wide slurred S wave in lead I

INCOMPLETE RBB



RBBB is described as incomplete when there is a pattern of RSR' in V1 to V3, with the QRS measuring less than 120 ms.

If the patient is a child, this pattern is often normal. It must be noted that this pattern may also be linked to Brugada syndrome, that is indicative of harmful ventricular arrhythmias.

Bifascicular and Trifascicular Block

1. Bifascicular Block

- **Definition**: Conduction block affecting **two fascicles** of the ventricular conduction system.
  - Most commonly:
    - **Right bundle branch block (RBBB) + Left anterior fascicular block (LAFB).**
    - **RBBB + Left posterior fascicular block (LPFB).**
- **ECG Findings**:
  - **RBBB**:
    - Wide QRS complex >120 ms.
    - rsR' pattern in V1 (rabbit ears) and broad S wave in lead I and V6.
  - **LAFB**:
    - Left axis deviation (QRS axis between -30° and -90°).
    - Small R waves in inferior leads (II, III, aVF) with deep S waves.
  - **LPFB**:
    - Right axis deviation (+90° to +180°).
    - Small R waves in leads I and aVL with deep S waves in the same leads.
- **Clinical Significance**:
  - **May indicate underlying structural heart disease.**
  - Increased risk of **progression to complete heart block.**
  - Often asymptomatic, but may present with **syncope** or **presyncope.**

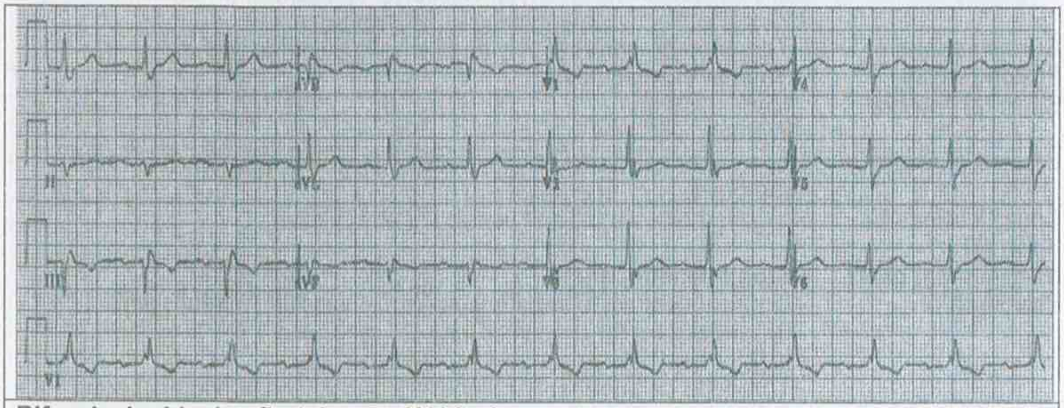
- **Management:**
  - Monitor patients, especially those with syncope or heart disease.
  - Consider pacemaker if symptomatic or if progression is anticipated.

2. Trifascicular Block

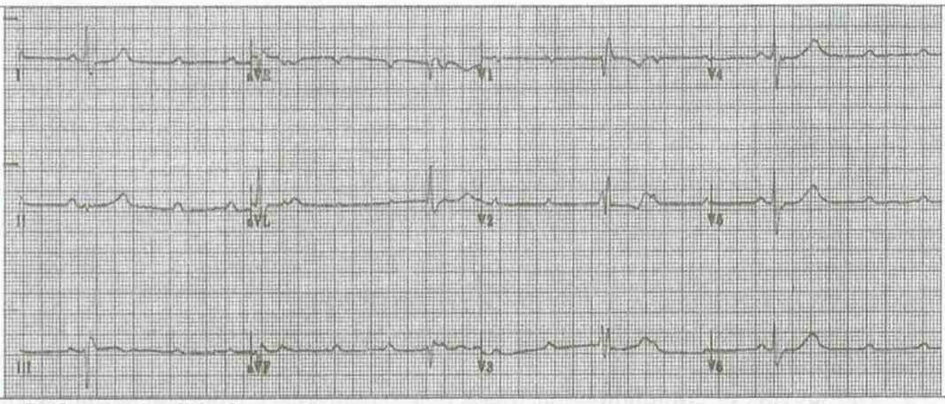
- **Definition**: Involves **conduction delay in all three fascicles**:
  - **RBBB + LAFB/LPFB + prolonged PR interval** (1st degree AV block).
- **ECG Findings**:
  - **RBBB** features: Wide QRS, rsR' in V1.
  - **LAFB or LPFB** features: Axis deviation (left or right).
  - **Prolonged PR interval** >200 ms (indicating 1st degree AV block).
- **Clinical Significance**:
  - **Higher risk of complete heart block** due to near-total conduction system failure.
  - May present with **syncope** or **presyncope**.
  - Often requires **pacemaker implantation** to prevent progression to complete heart block.
- **Management:**
  - **Pacemaker implantation** recommended due to high risk of complete heart block.
  - Monitor closely for signs of syncope or worsening conduction.

Comparison of Bifascicular and Trifascicular Block

Feature	Bifascicular Block	Trifascicular Block
Definition	Block in two fascicles	Block in all three fascicles
ECG Findings	RBBB + LAFB/LPFB	RBBB + LAFB/LPFB + Prolonged PR interval
Clinical Significance	May progress to complete heart block	Higher risk of complete heart block
Symptoms	Often asymptomatic, syncope or presyncope	More likely to cause syncope
Management	Monitor for progression	May require pacemaker implantation



Bifascicular block + first degree AV block
- **Right bundle branch block**
- **Left axis deviation (= left anterior fascicular block)**
- **First degree AV block**



True Trifascicular Block:

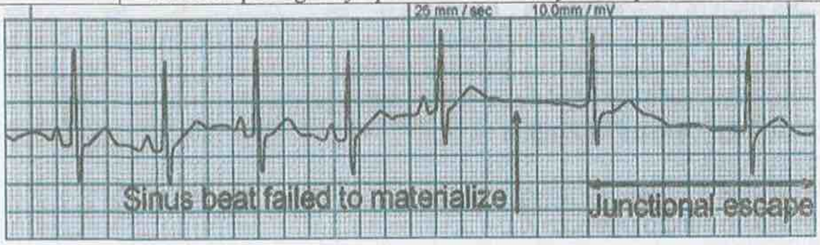
- **Right bundle branch block**
- **Left axis deviation (Left anterior fascicular block)**
- **Third degree heart block**

QT Interval

Parameter	Details
Definition	Time from the start of Q wave to the end of the T wave on ECG, indicating ventricular activity.
Normal Values	- **Men**: ≤ 440 ms - **Women**: ≤ 460 ms - **Children**: Varies with age and heart rate
QTc (Corrected QT Interval)	Adjusted for heart rate using **Bazett's formula**: $QTc = QT/\sqrt{RR}$
Prolonged QT Interval	- **Men**: > 450 ms - **Women**: > 470 ms
Causes of Prolonged QT	- **Congenital**: Long QT syndrome (e.g., Romano-Ward, Jervell and Lange-Nielsen) - **Acquired**: Medications (antiarrhythmics, antipsychotics, antidepressants, macrolides), electrolyte imbalances (hypokalemia, hypocalcemia, hypomagnesemia), MI, hypothermia
Complications of Prolonged QT	- **Torsades de pointes** (polymorphic ventricular tachycardia) - **Sudden cardiac death**
Short QT Interval	- **Men**: < 350 ms - **Women**: < 360 ms
Causes of Short QT	Hypercalcemia, hyperkalemia, acidosis, genetic conditions (short QT syndrome)
Complications of Short QT	Increased risk of atrial and ventricular arrhythmias
Management of QT Prolongation	- **Stop offending drugs** - **Correct electrolyte imbalances** (e.g., potassium, magnesium) - **Beta-blockers** for congenital long QT syndrome - **ICD** for high-risk congenital long QT syndrome - **Torsades de pointes**: IV magnesium sulfate and temporary pacing
Clinical Importance	- QT interval helps assess arrhythmia risk. - **QT prolongation** can lead to life-threatening arrhythmias and sudden cardiac death.
Monitoring	Regular ECG monitoring when on QT-prolonging medications.

ECG: Junctional escape rhythm

Parameter	Details
Definition	Abnormal heart rhythm originating from the AV node or adjacent area.
Heart Rate	40 to 60 beats per minute (bpm).
ECG Features	- **Absent P waves** - **Narrow QRS complexes** - Retrograde P waves (may appear before or after QRS complex).
Pulse Characteristics	Slow, regular pulse rate.
Triggering Factor	Common after a **pause** in the underlying rhythm.
Clinical Significance	Can act as a protective mechanism to maintain cardiac output during sinus arrest or block.
Management	- Address underlying causes (e.g., electrolyte imbalance, drug effect). - Consider pacing if symptomatic and bradycardia persists.



ECG: U wave

Causes of prominent U waves are:

- Hypokalaemia
- Cardiovascular drugs, e.g. digitalis, quinidine, amiodarone
- Psychotropic drugs, e.g. phenothiazines, tricyclic antidepressants.

Vascular lesions

Angina pectoris

Definition

- Angina pectoris is **chest discomfort** caused by **myocardial ischemia**, resulting from an imbalance between **oxygen supply and demand** in the heart.

Diagnostic Steps

Step 1: Assessing Chest Pain (Anginal Criteria)

Criteria	Description
Constricting discomfort	Front of the chest, or radiating to neck, jaw, shoulders, or arms.
Triggered by exertion	Brought on by physical activity.
Relief with rest or GTN	Pain relieved within 5 minutes by rest or glyceryl trinitrate.

- **Classification of Chest Pain:**
  - **Typical Angina**: All 3 criteria present.
  - **Atypical Angina**: 2 of the 3 criteria present.
  - **Non-anginal Pain**: 1 or none of the criteria present.

Non-Atherosclerotic Causes of Angina

- **Thyrotoxicosis**
- **Aortic stenosis or regurgitation**
- **Hypertrophic cardiomyopathy**
- **Anaemia**

Chest Pain Less Likely to Be Angina

- Continuous or prolonged pain.
- Unrelated to physical activity.
- Triggered by breathing.
- Associated with **dizziness, palpitations**, or **difficulty swallowing**.

Investigations and Diagnostic Pathway

Test	Purpose/Findings
12-lead ECG	Detects **ST depression** or **T-wave inversion** during symptoms. Normal ECG does not exclude angina.
Chest X-ray	Rules out other causes like **aortic aneurysm** or fractures.
Troponin Levels	Evaluate for possible ACS (acute coronary syndrome).
Echocardiogram	Detects **wall motion abnormalities** and structural disease (e.g., LV hypertrophy).

Probability Assessment for CAD

- **<10% Pretest Probability**: Low likelihood of CAD; minimal further testing needed.
- **≥10% Pretest Probability**: Intermediate to high risk, requiring further testing.

Additional Investigations for Stable Angina

Risk Group	Recommended Test
Low-risk (<10%)	**Exercise treadmill test** or **calcium scan** to rule out CAD.
Intermediate/High-risk (≥10%)	**Stress testing with imaging** (e.g., MPI, CMR, or stress echocardiography).
Renal impairment (GFR <30 ml/min)	**Dobutamine stress echocardiography** instead of MRI or MPI.

Management Approach for Angina

1. **Lifestyle Modifications**:
   - **Diet**: Mediterranean diet.
   - **Exercise**: Daily exercise until slightly breathless.
2. **Medical Management**:
   - **First-line**: Beta-blockers or calcium channel blockers.
   - **Second-line**: Dual therapy (beta-blocker + calcium channel blocker).
   - **Third-line**: Long-acting nitrates, ivabradine, nicorandil, or ranolazine.
3. **Surgical Interventions**:
   - **Coronary Artery Bypass Graft (CABG)** for significant CAD or multi-vessel disease.

Medications for Angina

Drug	Indications	Notes
Glyceryl Trinitrate (GTN)	Acute angina attacks	Sublingual spray or tablet.
Ivabradine	Heart failure or intolerant to beta-blockers	Lowers heart rate by inhibiting the If channel.
Long-acting Nitrates	Adjunct in chronic angina	Risk of tolerance—dose spacing recommended.

Definition of Significant CAD

- **≥70% stenosis** in a major coronary artery or **≥50% stenosis** in the left main coronary artery on coronary angiography.

Diagnostic steps:

Step	Description	Details
Step 1	Assess typicality of chest pain	Check for **constricting discomfort**, triggered by **physical exertion**, and **relieved by rest or GTN**. Classify as **typical, atypical, or non-anginal** based on these criteria.
Step 2	Perform a 12-lead ECG	Look for **J point/ST-segment depression** or **T-wave abnormalities** during symptoms. Pathological **Q waves** or **LBBB** may indicate previous infarction or CAD.
Step 3	Conduct a chest X-ray	Screen for **non-cardiac causes** of chest pain, such as an **enlarged aorta** or **rib fractures**.
Step 4	Estimate pretest probability of CAD	Use patient **age, sex, clinical history**, and risk factors to categorize as **low (<10%)** or **high (≥10%)** probability.
Step 5	Troponin and Echocardiogram	If ACS is suspected, measure **high-sensitivity troponins**. Use **echocardiography** to detect **wall motion abnormalities** or non-atherosclerotic causes (e.g., LV hypertrophy).
Step 6	CT Coronary Angiography (CTCA)	**First-line investigation** for CAD diagnosis to assess for coronary artery stenosis.

Step	Description	Details

Step 7	Further investigations if stable angina cannot be excluded	• **Low (<10%) probability**:
		  ○ No further testing unless suspicion persists.
		  ○ Perform **exercise treadmill test** (negative result rules out CAD).
		  ○ **Coronary calcium scan**: Absence of calcification makes CAD unlikely.
		• **Intermediate/High (≥10%) probability**:
		  ○ **Stress testing with imaging**:
		    ▪ **MPI** with exercise or pharmacologic stress (e.g., vasodilators).
		    ▪ **Dobutamine stress echocardiography**.
		    ▪ **Stress cardiac MRI** (avoid with GFR <30 mls/min).
		▫ **CCTA**: An option if non-invasive tests are inconclusive.

Patients with angina and/or dyspnoea and suspected coronary artery disease

ESC European Society of Cardiology

Pre-test probability of coronary artery disease

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	**M**	**W**	**M**	**W**	**M**	**W**	**M**	**W**
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

- **<10 percent → Low pretest probability**
- **≥10 percent → Intermediate/high pretest probability**

Drug management

Key Medications

1. **Aspirin and Statin**: For all patients unless contraindicated.
2. **Sublingual Glyceryl Trinitrate (GTN)**: To relieve acute angina attacks.

Stepwise Medical Management

Step	Treatment	Details
1st Line	Monotherapy	**Beta-blocker** or **calcium channel blocker**. ▫ Calcium channel blocker options: Verapamil, Diltiazem. ▫ Avoid beta-blocker + verapamil (risk of heart block). ▫ Increase dosage to maximum tolerated if initial response is inadequate.
2nd Line	Dual Therapy	Combine **beta-blocker** with **calcium channel blocker**. If intolerant to dual therapy, consider **long-acting nitrate**, **ivabradine**, **nicorandil**, or **ranolazine**.
3rd Line	Triple Therapy	Add a third drug only if awaiting **PCI** or **CABG**. • CABG indicated for: 1. Significant left main disease 2. Three-vessel disease 3. Two-vessel disease with abnormal LV function or LAD involvement.

Surgical Interventions

- **Coronary Artery Bypass Graft (CABG)**:
  - **Approaches**:
    1. Use of the **internal thoracic artery** to bypass LAD.
    2. Use of the **great saphenous vein** to bypass obstructed arteries.

A beta-blocker or a calcium channel blocker is used first-line to prevent angina attacks

You should still use bisoprolol in patients with COPD and IHD, because it carries an important outcome benefit

Nitrates: Mechanism, Side Effects, and Use

Type	Dose & Use	Mechanism	Side Effects	Contraindications
Glyceryl Trinitrate	Sublingual: 500-600 mcg; IV infusion: 10–200 mcg/min	**Vasodilator**, reduces **venous return**, decreases LV workload	Flushing, headache, hypotension	Aortic/mitral stenosis, tamponade, hypovolaemia
Isosorbide Dinitrate	Oral: 30–120 mg daily; IV: 2–10 mg/hour	Used for **angina prophylaxis**		
Isosorbide Mononitrate	Oral: 10 mg twice daily, up to 120 mg daily	Adjunct in **CHF** or **angina prophylaxis**		

Ivabradine Overview

Mechanism	Indications	Dose	Adverse Effects	Contraindications
Inhibits If channels in the sinoatrial node, reducing heart rate	Stable angina, Heart failure (NYHA II-IV, EF ≤35%)	Start: 2.5-5 mg twice daily, increase to 7.5 mg if needed	Visual disturbances (luminous phenomena), bradycardia	Acute MI, heart failure, cardiogenic shock, low HR (<70 bpm for angina, <75 bpm for HF)

Acute coronary syndrome (ACS)

Definition

ACS refers to a group of clinical conditions caused by **reduced blood flow to the heart**, leading to myocardial ischemia or infarction. It classified it to 3 types:

1. **ST-Elevation Myocardial Infarction (STEMI)**: Full-thickness myocardial injury with ECG showing ST-elevation.
2. **Non-ST-Elevation Myocardial Infarction (NSTEMI)**: Partial-thickness injury with elevated cardiac biomarkers but no ST elevation on ECG.
3. **Unstable Angina**: Myocardial ischemia without biomarkers of infarction.

Comparison of STEMI, NSTEMI, and Unstable Angina

Feature	STEMI	NSTEMI	Unstable Angina
Definition	Full-thickness myocardial infarction with complete occlusion of a coronary artery.	Partial-thickness myocardial infarction caused by a non-occlusive thrombus.	Myocardial ischemia without infarction or biomarker elevation.
ECG Findings	ST-segment elevation or new left bundle branch block (LBBB).	ST-segment depression or T-wave inversion (without ST elevation).	May show non-specific changes or be normal.
Cardiac Biomarkers	Elevated troponins (indicating myocardial injury).	Elevated troponins.	No elevation in cardiac biomarkers.
Clinical Presentation	Severe, persistent chest pain, often radiating to arm, neck, or jaw.	Similar to STEMI but less severe or prolonged.	Chest pain or discomfort, typically during rest or with minimal exertion.
Pathophysiology	Complete coronary artery occlusion due to a ruptured plaque and thrombus.	Partial occlusion with myocardial injury but not full-thickness infarction.	Transient ischemia without myocardial necrosis.

Feature	STEMI	NSTEMI	Unstable Angina
Treatment Approach	**Primary PCI** (first-line) or thrombolysis if PCI unavailable within 120 minutes.	Antiplatelet and anticoagulant therapy, with PCI often performed.	Symptom management, antiplatelets, and medical therapy without revascularization unless needed.
Reperfusion Therapy	Urgent PCI or fibrinolysis.	PCI indicated within 24–72 hours.	No immediate reperfusion therapy required.
Prognosis	High risk of complications (e.g., arrhythmias, heart failure).	Intermediate risk of recurrent events and complications.	Low to intermediate risk, depending on other factors.

Myocardial Infarction (MI)

Definition and Classification

1. **Definition**: MI refers to **myocardial ischemia** caused by **coronary artery blockage**, leading to heart muscle damage.
2. **Clinical Classification** (NICE 2010):
   - **Type 1 MI**: Ischemia due to a **primary coronary event** (e.g., plaque rupture, fissuring, or dissection).
   - **Type 2 MI**: Ischemia from **increased oxygen demand** or **reduced supply** (e.g., coronary spasm, embolism, anaemia, arrhythmias, hypertension).

Clinical Features

- **Jaw pain radiation**: A **specific indicator** of myocardial ischemia.
- **Precipitating factors**:
  - Physical exertion
  - Rest or sleep
  - Surgical procedures
  - Emotional stress

Diurnal Variation in Ischemia

- **STEMI incidence** peaks between **8-9 am**, associated with:
  - ↑ **Adrenergic activity**
  - ↑ **Platelet adhesiveness**
  - ↑ **Plasma fibrinogen levels**
  - ↓ **Fibrinolysis**
- **NSTEMIs** do not follow this diurnal pattern.

Risk Factors

- **Post-surgical MI**: Highest risk occurs **72 hours post-operation**.
- **Diabetic patients**: May experience silent MIs due to **autonomic dysfunction**.

Investigations

1. **ECG (Electrocardiogram)**:
   - **Best initial test**; should be performed immediately.
   - A normal ECG does **not exclude MI**.
2. **Cardiac Troponin Levels**:
   - Measure immediately and repeat after **1–6 hours**.
   - Troponins confirm myocardial injury.
3. **Transthoracic Echocardiography**:

- Performed if diagnosis is unclear.
- Findings:
  - **Wall motion abnormalities**
  - **Reduced left ventricular function**

ECG localization of STEMI

ECG leads with ST elevation	Infarction location
V1 – V2	Anteroseptal (LAD)
V3- V4	Antero-apical (distal LAD)
V5- V6	Antero-lateral (LAD or LCX)
I, aVL	Lateral (LCX)
II, III, aVF	Inferior (RCA)
V7 – V9, ST depression V1- V3 with tall R waves	Posterior (PDA)

> Primary percutaneous coronary intervention is the gold-standard treatment for ST-elevation myocardial infarction

Myocardial Infarction: Management

Emergent Therapy

1. **Symptom Relief**:
   - **Glyceryl Trinitrate (GTN)**:
     - **Sublingual GTN** with **morphine + metoclopramide** to relieve pain.
     - If pain persists, use **IV GTN** to manage ongoing myocardial ischemia.
2. **Antiplatelet Therapy**:
   - **Aspirin 300 mg**: Standard initial treatment for all patients unless contraindicated.
   - Add a **second antiplatelet** (e.g., **ticagrelor, clopidogrel, or prasugrel**).
     - **Aspirin + Ticagrelor** (300 mg + 180 mg) provides better outcomes than aspirin + clopidogrel.
     - **NICE** recommends that additional antiplatelets should only be initiated in hospital.
3. **Anticoagulation**:
   - Use **bivalirudin** (direct thrombin inhibitor) along with aspirin and clopidogrel.
   - **Heparin** (either low-molecular weight or unfractionated) is also used to prevent thrombosis.
4. **Oxygen Therapy**:
   - Administer oxygen only if **SpO_2 < 94%** (unless the patient is at risk of hypercapnic failure).
   - In **COPD** patients, aim for **88-92%** SpO_2 until blood gas analysis is available.
   - Routine oxygen is **not recommended** for $SpO_2 \geq 90\%$ (ESC 2017 guidelines).
5. **Analgesia**:
   - Use **morphine** for pain relief if the patient has apparent pain.

Reperfusion Therapy

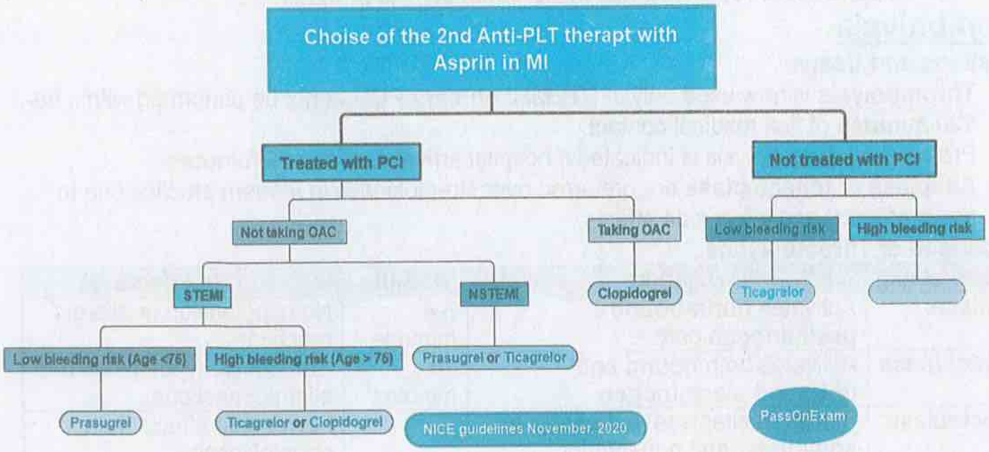
- **Primary PCI**:
  - **First-line treatment** for restoring myocardial perfusion within **12 hours** of symptom onset.

  - **Rescue PCI** is recommended if thrombolysis fails (e.g., no ST resolution 90 minutes post-thrombolysis).
- **Thrombolysis (Fibrinolysis)**:
  - Indicated if PCI is unavailable within **120 minutes**.
  - After thrombolysis, if symptoms persist or ECG shows no resolution, transfer the patient for **PCI**.

Adjuvant Therapies Post-Reperfusion

- **Beta-blockers**:
  - Early use helps **reduce infarct size** by decreasing heart rate, blood pressure, and contractility.
  - Beta-blockers can also prevent early **ventricular fibrillation** episodes.
- **ACE Inhibitors**:
  - Recommended for patients with **significant left ventricular dysfunction** to improve cardiac remodeling and prevent heart failure

.



Percutaneous Coronary Intervention (PCI)

Definition

- PCI is a **revascularization technique** used to restore blood flow in the coronary arteries for patients with **ischemic heart disease** (stable angina or acute coronary syndromes).
- **Stents** are deployed in 95% of cases to prevent reocclusion—balloon angioplasty alone is now rare.

Stent Types

1. **Bare-Metal Stents (BMS)**:
   - Simple metal stents; associated with a higher risk of **restenosis**.
2. **Drug-Eluting Stents (DES)**:
   - Coated with **paclitaxel or rapamycin** to inhibit tissue growth and reduce restenosis.
   - Slower endothelization increases the risk of **thrombosis**.

Post-Stent Care

- **Dual Antiplatelet Therapy (DAPT)** with **aspirin and clopidogrel** is essential to prevent stent thrombosis.
  - **Aspirin**: Continued **indefinitely**.

- **Clopidogrel**: Recommended for **12 months**, especially with DES.
- **Early cessation** of DAPT increases the risk of ischemic events and stent thrombosis, with **high morbidity (42%) and mortality (71%)** in DES thrombosis.

Surgery Post-PCI

- **Elective surgery** should be postponed for 12 months to safely discontinue clopidogrel and continue aspirin.

Complications

1. **Stent Thrombosis**:
   - Occurs in **1-2%** of patients, often in the **first month**.
   - Presents as **acute myocardial infarction**; treated with **primary angioplasty**.
2. **Restenosis**:
   - Due to **tissue proliferation** around the stent, typically within **3-6 months**.
   - **Risk factors**: Diabetes, renal impairment, and venous bypass grafts.
   - **Uncoated stents** have a 40-50% restenosis rate in diabetic patients.
   - **DES** reduces restenosis risk by 80% with continued DAPT.

Thrombolysis

Indications and Usage

- **Thrombolysis** is now used only in **STEMI** if **primary PCI** cannot be performed within **90-120 minutes** of first medical contact.
- Pre-hospital thrombolysis is indicated if hospital arrival exceeds **30 minutes**.
- **Alteplase or tenecteplase** are preferred over streptokinase in modern practice due to better efficacy and fewer side effects.

Comparison of Thrombolytics

Thrombolytic	Action	Half-life	Side Effects
Alteplase	Activates **fibrin-bound plasminogen** only.	3-4 minutes	No hypotension or allergic reactions.
Streptokinase	Activates both **bound and unbound plasminogen**.	18 minutes	Can cause hypotension and allergic reactions.
Tenecteplase	Similar to alteplase, but **easier to administer** and non-inferior.	-	Fewer side effects than streptokinase.

ECG Criteria for Thrombolysis

- **ST elevation**:
  - 1 mm in **two contiguous limb leads**.
  - 2 mm in **two contiguous chest leads**.
- **New left bundle branch block**.

Post-Thrombolysis Monitoring and Rescue PCI

- **ECG at 90 minutes** post-thrombolysis: Check for >50% reduction in ST elevation.
- If no improvement, **rescue PCI** is preferred over repeated thrombolysis.
- PCI is beneficial even after successful thrombolysis to reduce ischemic events.

Contraindications to Thrombolysis

- **Absolute contraindications**:
  - Recent GI or vaginal bleeding.
  - History of hemorrhagic stroke or ischemic stroke in the last 6 months.
  - Uncontrolled hypertension or recent trauma/surgery.
  - Known **bleeding disorder** or prolonged CPR (>30 minutes).
  - **Aortic dissection** or **lumbar puncture** within the last week.
- **Relative contraindications**:
  - Diabetic retinopathy, known allergy, or anticoagulant therapy.
  - Risk factors for bleeding: **Age, renal impairment**, low body weight.

Thrombolysis is no longer indicated except in the context of **STEMI** where **PCI** is not available within 90 minutes of first medical contact.

Management of Hyperglycemia in ACS
- Use **intravenous insulin infusion** to maintain blood glucose <11 mmol/L.
- **Metformin** should be stopped to prevent lactic acidosis risk.

Complications
MI Complications and Key Features

Complication	Description
Cardiac Arrhythmias	Occur within the first few days post-MI. **Ventricular fibrillation** is the most common cause of early death. **AV block** is more frequent after inferior MI.
Left Ventricular (LV) Failure & Pulmonary Oedema	Can result from LV infarction, ventricular septal defect (VSD), or papillary muscle rupture leading to mitral regurgitation.
Post-infarction Pericarditis	Occurs **1-3 days** post-MI; presents with **friction rub** on auscultation.
Papillary Muscle Rupture	Develops **2-7 days** post-MI. Causes **acute mitral regurgitation** with pulmonary oedema and a loud systolic murmur. Requires **emergency surgical repair**.
Interventricular Septal Rupture	Occurs **3-5 days** post-MI due to **macrophage-mediated degradation**, leading to a VSD and acute heart failure. Presents with a pan-systolic murmur. Urgent surgery is needed.
Ventricular Pseudoaneurysm	Forms **3-14 days** post-MI when the ventricular wall rupture is contained by pericardium or scar tissue. Increases risk of **thromboembolism and arrhythmias**.
True Ventricular Aneurysm	Develops **2 weeks to several months** after MI. Associated with **persistent ST elevation** and LV failure. Thrombus formation may increase the risk of stroke.
Ventricular Free Wall Rupture	Occurs **5-14 days** post-MI, leading to **cardiac tamponade** (raised JVP, pulsus paradoxus). Requires urgent **pericardiocentesis and thoracotomy**.
Dressler Syndrome	Autoimmune pericarditis occurring **weeks post-MI**. Presents with **fever, pleuritic chest pain, pericardial effusion**, and raised ESR. Treated with **NSAIDs**.
Chronic Heart Failure	Develops due to **systolic dysfunction**. LV failure is a key predictor of poor long-term outcomes post-STEMI.

Primary Prevention of Cardiovascular Events: Key Medications

1. **ACE Inhibitors**:
    - Lower blood pressure and reduce cardiovascular risk.
    - **Blood pressure control** has a greater impact on reducing cardiovascular events than managing diabetes or lipids.
2. **Aspirin**:
    - Low-dose aspirin helps prevent thrombotic events, particularly in individuals with high cardiovascular risk.
3. **Metformin**:
    - Recommended for **overweight diabetic patients**.
    - Lowers the risk of myocardial infarction (MI) by **40%**, compared to other antidiabetic therapies such as sulphonylureas or insulin.
4. **Statins**:
    - Effective in **lowering cholesterol** and reducing the risk of heart attacks and strokes.

Secondary Prevention: Medications for All Patients Post-MI

1. **Dual Antiplatelet Therapy (DAPT)**:
    - **Aspirin** + a second antiplatelet agent (e.g., clopidogrel or ticagrelor) for 12 months.
    - **STEMI**: DAPT (aspirin + clopidogrel) is recommended for 12 months (ESC guidelines).
    - **NSTEMI**: Clopidogrel for 12 months following the NICE 2013 guidelines.
2. **ACE Inhibitor**: Reduces mortality and prevents cardiac remodeling.
3. **Beta-blocker**: Reduces the risk of reinfarction and arrhythmias.
4. **Statin**: For long-term cholesterol management and prevention of future events.

Lifestyle Modifications

1. **Diet**:
    - Encourage a **Mediterranean-style diet** (plant-based oils instead of butter/cheese).
    - Omega-3 supplements or oily fish are **not recommended**.
2. **Exercise**:
    - Advise **20-30 minutes** of exercise daily to the point of being "slightly breathless."
3. **Sexual Activity**:
    - May resume **4 weeks after an uncomplicated MI**.
    - **PDE5 inhibitors** (e.g., sildenafil) can be used after 6 months but must be avoided if the patient is on **nitrates or nicorandil**.

Additional Therapies

- **Aldosterone Antagonists** (e.g., eplerenone):
    - For patients with **heart failure** or **left ventricular systolic dysfunction**.
    - Initiate **3-14 days post-MI** following ACE inhibitor therapy.

Subclavian steal syndrome

Definition

- Subclavian steal syndrome occurs when **stenosis or occlusion** of the **subclavian artery** proximal to the origin of the **vertebral artery** causes **reversed blood flow** through the vertebral artery, "stealing" blood from the brain to supply the affected arm.

Pathophysiology

- **Stenosis or occlusion** in the subclavian artery results in:
  - **Reversal of flow** in the ipsilateral vertebral artery.
  - Blood is "stolen" from the cerebral circulation to supply the arm, especially during exertion.
  - Reduced blood supply to the posterior cerebral circulation can cause **neurological symptoms**.

Causes

- **Atherosclerosis** (most common cause).
- **Takayasu arteritis**.
- **Thoracic outlet syndrome**.
- Trauma, radiation, or surgical injury.

Clinical Features

1. **Neurological Symptoms** (due to vertebrobasilar insufficiency):
   - Dizziness or vertigo.
   - Syncope or near-syncope.
   - Visual disturbances (blurred vision, diplopia).
   - Ataxia or unsteady gait.
2. **Upper Limb Symptoms** (due to arm ischemia):
   - Weakness or fatigue in the arm, especially with exertion.
   - Arm pain or claudication.
   - **Pulse discrepancy**: reduced or absent radial pulse on the affected side.
   - **Blood pressure difference** >10-15 mmHg between arms.

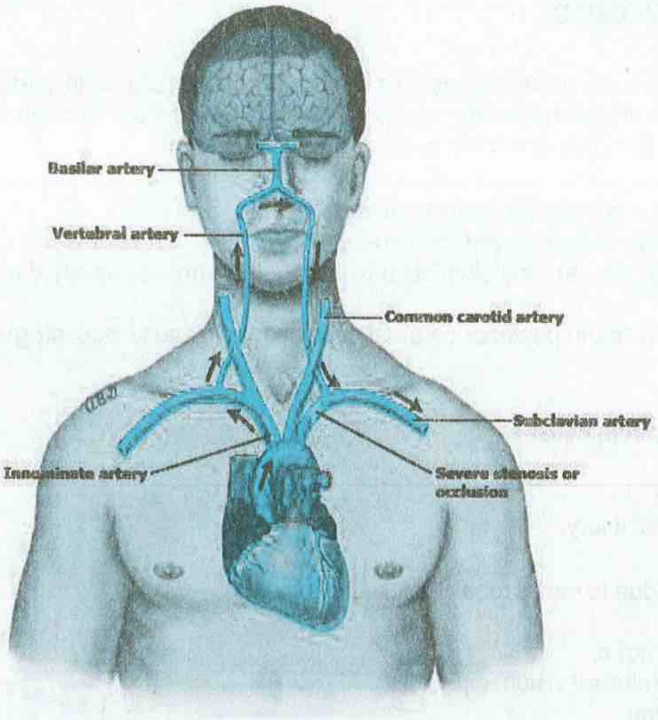
Diagnosis

- **Blood pressure measurement** in both arms (significant discrepancy suggests the syndrome).
- **Doppler ultrasound**: reveals reversed flow in the vertebral artery.
- **CT angiography (CTA)** or **MR angiography (MRA)**: identifies the site and severity of subclavian artery stenosis.
- **Conventional angiography** (gold standard): confirms the diagnosis and helps plan interventions.

Management

1. **Lifestyle modifications and medical management**:
   - Manage risk factors (e.g., **hypertension, hyperlipidemia, diabetes**).
   - **Antiplatelet therapy** (e.g., aspirin) to reduce thrombotic risk.
2. **Interventional or Surgical Treatment**:
   - **Percutaneous angioplasty with stenting** for significant stenosis.
   - **Bypass surgery** or **subclavian artery endarterectomy** for complex cases.

> **Brainstem features** (vertigo, diplopia, dysarthria, and drop attacks) **with disparity in BP > 15 mm Hg and pain precipitated by exercise → Subclavian steal syndrome**



Pathophysiology of subclavian steal syndrome

Under normal conditions, the subclavian artery distributes blood equally to the arteries in the brain and arms (A). If there is stenosis of the subclavian artery proximal to the origin of the vertebral artery, this leads to hypoperfusion of the upper extremities on the affected side (B). This is compensated by a contralateral circulation, in which there is increased blood flow from the unaffected side to the affected side via the vertebral arteries. As a result, there is hypoperfusion of the vertebrobasilar territory and corresponding central nervous system symptoms.

Peripheral vascular disease

Definition

- Peripheral vascular disease refers to **obstruction or narrowing** of the **arteries** (peripheral arteries) outside of the heart and brain, primarily affecting the **legs**. It is a type of **arterial disease** that limits blood flow to the limbs.

Causes and Risk Factors

- **Atherosclerosis** (most common cause).
- **Smoking**.
- **Diabetes mellitus**.
- **Hypertension**.
- **Hyperlipidemia**.
- Age >60 years.
- **Sedentary lifestyle** and **obesity**.

Clinical Features

1. **Intermittent Claudication**:
   - Pain or cramping in the calf, thigh, or buttocks during exercise that resolves with rest.
2. **Critical Limb Ischemia**:
   - Persistent pain at rest, particularly at night.
   - Non-healing ulcers or sores on the legs or feet.
   - Gangrene (in severe cases).
3. **Physical Signs**:
   - **Diminished or absent peripheral pulses**.
   - **Cool, pale skin**.
   - **Hair loss** on the legs and feet.
   - **Shiny skin** with delayed capillary refill.
   - **Dependent rubor**: redness when the limb is lowered.

Diagnosis

- **Ankle-brachial index (ABI)**:
  - ABI < 0.9 indicates PVD.
- **Doppler ultrasound**: assesses blood flow and detects blockages.
- **CT or MR angiography**: identifies the location and extent of arterial disease.
- **Conventional angiography** (gold standard): used for planning interventions.

Management

1. **Lifestyle Modifications**:
   - **Smoking cessation**.
   - Control of **diabetes, hypertension, and hyperlipidemia**.
   - Regular **exercise**: supervised walking programs improve claudication symptoms.
2. **Medications**:
   - **Antiplatelet agents** (e.g., aspirin, clopidogrel) to prevent thrombotic events.
   - **Statins** to reduce cardiovascular risk.
   - **Cilostazol**: improves walking distance in claudication.
3. **Surgical and Interventional Options**:
   - **Angioplasty with stenting** for localized arterial narrowing.
   - **Bypass surgery** for severe or widespread blockages.
   - **Amputation** in cases of non-salvageable limb due to gangrene or infection.

Complications

- **Critical limb ischemia**.
- **Infections** of ulcers or sores.
- **Amputation** due to gangrene.
- **Increased risk** of myocardial infarction and stroke.

Comparison: Differential Diagnosis of Foot Ulcers

Cause	Clinical Features	Location	Key Findings	Management
Arterial Ulcers	- Painful, worse with elevation. - Intermittent claudication.	Tips of toes, heel, pressure points	- Cool, pale skin. - Absent/diminished pulses. - Well-demarcated edges.	Improve perfusion: lifestyle changes, revascularization, antiplatelets.
Venous Ulcers	- Aching pain relieved by elevation. - Leg swelling.	Medial malleolus or lower leg.	- Edema, hyperpigmentation, varicosities. - Irregular borders, shallow.	Compression therapy, leg elevation, wound care.
Diabetic Ulcers	- Painless (due to neuropathy). - Recurrent infections.	Plantar aspect (pressure points).	- Callus formation around ulcer. - Peripheral neuropathy.	Glycemic control, offloading, wound care.
Pressure Ulcers	- Localized pain or tenderness. - Seen in immobile patients.	Bony prominences (heel, sacrum).	- Erythema, skin breakdown. - Can progress to deeper tissue damage.	Frequent repositioning, pressure relief, wound care.
Infectious Ulcers	- Purulent discharge, fever, warmth.	Any location.	- Signs of infection (erythema, warmth).	Antibiotics, wound debridement if needed.
Malignant Ulcers	- Non-healing ulcer, often enlarging. - May bleed easily.	Any site, often chronic scars.	- Irregular edges, possible nodularity.	Biopsy to confirm diagnosis, surgical resection.

Aortic aneurysms

Definition

- **Aortic aneurysm** refers to a localized **dilation of the aorta** where the diameter exceeds 50% of the normal size.

Types of Aortic Aneurysms

1. **Abdominal Aortic Aneurysm (AAA)**:
   - Commonly located **below the renal arteries**.
   - More frequent in **men** and **smokers**.
   - **Risk of rupture** increases with diameter (>5.5 cm).
2. **Thoracic Aortic Aneurysm (TAA)**:
   - Involves the **ascending, aortic arch, or descending thoracic aorta**.
   - Associated with **connective tissue disorders** (e.g., Marfan syndrome, Ehlers-Danlos).

Risk Factors

- **Atherosclerosis** (most common).
- **Smoking**.
- **Hypertension**.
- **Genetic disorders** (Marfan, Ehlers-Danlos).
- Age >65 years.
- Male gender.
- Family history of aortic aneurysm.

Clinical Features

- **Asymptomatic** (often detected incidentally).
- **Abdominal pain** or **back pain** (AAA).
- **Chest pain** (TAA).
- Pulsatile abdominal mass (in AAA).
- Compression symptoms (e.g., hoarseness, dysphagia) in TAA.

Complications

1. **Rupture**:
   - Severe hypotension and shock.
   - High mortality rate, especially for ruptured AAA.
2. **Dissection**:
   - Tearing chest pain radiating to the back.
   - More common with TAA.

Diagnosis

- **Ultrasound**: First-line for screening and monitoring AAA.
- **CT angiography**: Accurate for both TAA and AAA.
- **MRI**: Useful for anatomical details, especially in thoracic aneurysms.
- **Chest X-ray**: May show widened mediastinum in TAA.

Management

1. **Medical Management**:
   - **Blood pressure control**: Beta-blockers, ACE inhibitors.
   - **Smoking cessation**.
   - Monitor small aneurysms with **regular imaging**.
2. **Surgical or Endovascular Repair**:
   - **Open surgery**: Large or symptomatic aneurysms.
   - **Endovascular Aneurysm Repair (EVAR)**: Less invasive option for AAA.
   - **Indications for repair**:
     - AAA > 5.5 cm.
     - TAA > 5.5-6 cm.
     - Rapid expansion (>0.5 cm/year).
     - Symptomatic aneurysms.

Screening

- **AAA screening**: Recommended for men aged **65-75 years** with a history of smoking.
- **Family history screening**: If a first-degree relative has an aortic aneurysm.

Prognosis

- **Small aneurysms**: Good prognosis with monitoring.
- **Ruptured aneurysms**: High mortality, emergency repair needed.

Abdominal vs. thoracic aortic aneurysm

Characteristics	Abdominal aortic aneurysm (AAA)	Thoracic aortic aneurysm (TAA)
Location	• Below the renal arteries (most common)	• Ascending aorta (most common)
Epidemiology	• Advanced age • Predominantly men • More common than TAA	• Advanced age • Predominantly men
Aetiology	• Smoking (most important risk factor) • Atherosclerosis • Hypercholesterolemia and arterial hypertension	• Arterial hypertension • Bicuspid aortic valve • Tertiary syphilis [10] • Connective tissue diseases (e.g., Marfan syndrome, Ehlers-Danlos syndrome) • Trauma • Smoking
Clinical features	• Pulsatile abdominal mass • Bruit on auscultation • Lower back pain	• Feeling of pressure in the chest • Thoracic back pain
Diagnostics	• Abdominal ultrasound (**best initial and confirmatory test**)	• Chest x-ray and CTA of chest
Therapy	• Control BP (B.blocker) • Indications for repair ⇨ **Diameter: ≥ 5.5 cm** ⇨ Expansion rate: ≥ 1 cm/year ⇨ Symptomatic aneurysm ⇨ Complications (e.g., rupture)	• Control BP (B.blocker) • Indications for repair ⇨ Diameter: ascending aneurysm ≥ 5.5 cm; descending aneurysm ≥ 6.5 cm ⇨ Expansion rate: ≥ 1 cm/year ⇨ Symptomatic aneurysm ⇨ Complications (e.g., rupture)

Aortic dissection

Definition

- **Aortic dissection** occurs when there is a **tear in the intimal layer** of the aorta, allowing blood to flow between the layers of the aortic wall, creating a **false lumen**.

Classification

1. **Stanford Classification**:
   - **Type A**: Involves the **ascending aorta** (with or without descending aorta).
   - **Type B**: Involves only the **descending aorta** (distal to the left subclavian artery).
2. **DeBakey Classification**:
   - **Type I**: Involves both ascending and descending aorta.
   - **Type II**: Limited to the ascending aorta.
   - **Type III**: Limited to the descending aorta.

Risk Factors

- **Hypertension** (most common).
- **Connective tissue disorders** (e.g., Marfan syndrome, Ehlers-Danlos syndrome).
- **Aortic aneurysm.**
- **Bicuspid aortic valve.**
- **Cocaine use.**
- **Trauma.**
- **Pregnancy** (increased risk in third trimester).

Clinical Features

- **Severe, tearing chest pain** radiating to the **back**.
- **Pulse deficits** (asymmetry between limbs).
- **Hypotension or shock** (if rupture or tamponade occurs).
- **Neurological symptoms** (e.g., syncope, stroke) if cerebral vessels are involved.
- **Aortic regurgitation murmur** (in Type A dissection).

Complications

1. **Rupture** → Cardiac tamponade, hemothorax.
2. **Aortic regurgitation** → Heart failure.
3. **Stroke** or **paraplegia** (due to vessel involvement).
4. **Ischemia** → Coronary, renal, or intestinal infarction.

Diagnosis

- **CT angiography (CTA)**: Gold standard for diagnosis.
- **Transesophageal echocardiography (TEE)**: Preferred in unstable patients.
- **MRI**: Accurate but less practical in emergencies.
- **Chest X-ray**: May show **widened mediastinum**.

Management

1. **Type A Dissection** (Ascending aorta):
    - **Emergency surgery**: Repair or replace the affected aorta.
    - Manage complications (e.g., tamponade, aortic regurgitation).
2. **Type B Dissection** (Descending aorta):
    - **Medical management** (if uncomplicated):
        - Blood pressure control (IV beta-blockers or vasodilators).
    - **Endovascular repair**: If complications (e.g., rupture, ischemia).

Medications

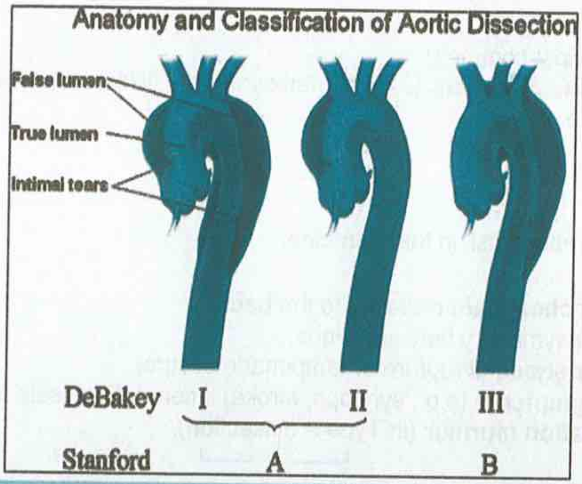
- **Beta-blockers**: First-line to reduce heart rate and blood pressure.
- **Vasodilators** (e.g., nitroprusside): For additional blood pressure control.
- **Analgesia**: To relieve severe pain.

Prognosis

- **Type A dissection**: High mortality without surgery.
- **Type B dissection**: Better prognosis with medical management if uncomplicated.
- **Complicated dissections**: High risk of rupture or organ ischemia if untreated.

Follow-up

- **Regular imaging**: To monitor the aortic diameter and detect progression.
- **Long-term blood pressure control**: Essential to prevent recurrence.



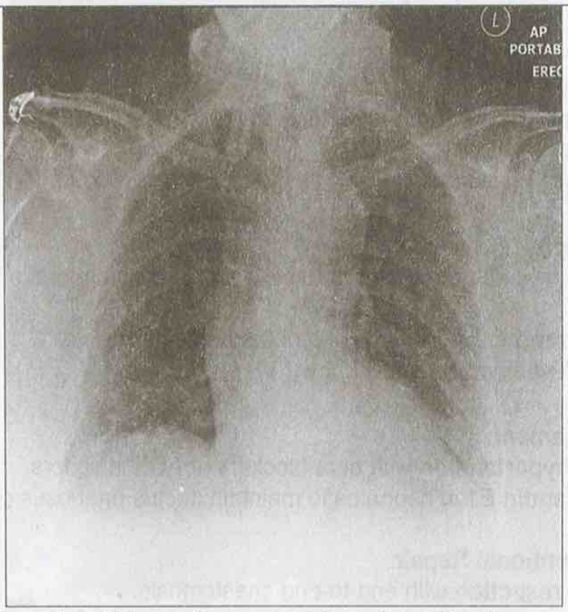
Aortic dissection

- type A - ascending aorta - control BP(IV labetalol) + surgery
- type B - descending aorta - control BP(IV labetalol)

Comparison: Type A vs. Type B Aortic Dissection

Feature	Type A Dissection	Type B Dissection
Location	Involves the **ascending aorta**, may extend to arch or descending aorta.	Limited to the **descending aorta** (distal to the left subclavian artery).
Stanford Classification	Type A	Type B
DeBakey Classification	Type I (ascending + descending) or Type II (ascending only).	Type III (descending only).
Clinical Presentation	Severe **chest pain** radiating to **back**; may cause **aortic regurgitation murmur**.	Severe **back pain**; less likely to cause heart involvement.
Complications	- **Aortic regurgitation** (heart failure). - **Cardiac tamponade** (if rupture occurs). - **Stroke** if cerebral vessels are involved.	- **Ischemia** of kidneys, intestines, or limbs. - **Rupture** into pleural or pericardial spaces (rare).
Management	**Emergency surgery** required to prevent fatal complications.	**Medical management** (blood pressure control) if uncomplicated. **Endovascular repair** if complications arise.
Mortality Risk	High without immediate surgery.	Better prognosis with medical therapy if uncomplicated.
Blood Pressure Control	Adjunct to surgery to stabilize the patient.	**First-line therapy** to manage uncomplicated cases.

Feature	Type A Dissection	Type B Dissection
Common Risk Factors	**Hypertension, bicuspid aortic valve**, Marfan syndrome, aortic aneurysm.	**Hypertension**, trauma, connective tissue disorders.



This chest X-ray shows a widened mediastinum

Coarctation of the aorta

Definition

- A **narrowing of the aorta**, typically near the **ductus arteriosus**, leading to **obstruction of blood flow** from the heart to the lower body.

Classification

1. **Preductal (Infantile Type)**:
   - Narrowing occurs **proximal to the ductus arteriosus.**
   - Often associated with **Patent Ductus Arteriosus (PDA).**
   - More severe; presents early in life.
2. **Postductal (Adult Type)**:
   - Narrowing occurs **distal to the ductus arteriosus.**
   - Manifests later in life, often with hypertension.

Risk Factors and Associations

- **Turner syndrome** (common genetic association).
- **Bicuspid aortic valve** (present in ~50% of cases).
- Family history of congenital heart disease.

Pathophysiology

- Narrowing of the aorta increases **afterload**, causing:
  - **Left ventricular hypertrophy (LVH).**
  - **Hypertension** in upper extremities.
  - **Hypoperfusion** of the lower body.

Clinical Features

- **Upper body**: Hypertension, headaches, epistaxis, and claudication.
- **Lower body**: Weak/absent femoral pulses, cold lower extremities, leg fatigue.
- **Infants**: Heart failure, respiratory distress, poor feeding.
- **Differential pulse and blood pressure**: Higher in upper extremities than lower.

Complications

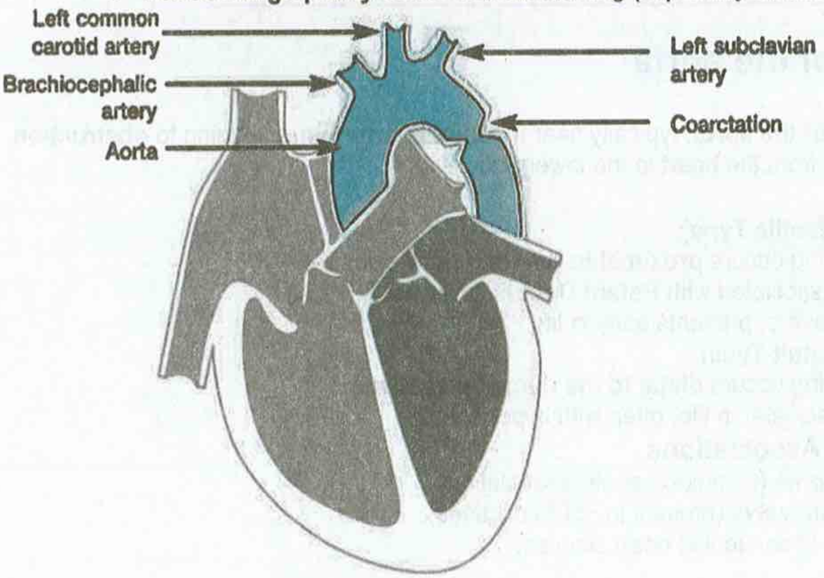
- **Heart failure.**
- **Aortic rupture or dissection.**
- **Intracranial hemorrhage** (from hypertension).
- **Endocarditis** or **infective aortitis**.
- **Claudication** and leg ischemia.

Investigations

- **Echocardiography**: Confirms diagnosis.
- **Chest X-ray**: Shows rib notching (due to collateral circulation) and a "3 sign" (indentation of the aorta).
- **CT/MRI angiography**: Detailed imaging of the aortic narrowing.
- **ECG**: Shows left ventricular hypertrophy (LVH).

Management

1. **Medical Management**:
   - **Control hypertension** with beta-blockers or ACE inhibitors.
   - **Prostaglandin E1** in neonates to maintain ductus arteriosus patency before surgery.
2. **Surgical/Interventional Repair**:
   - **Surgical resection** with end-to-end anastomosis.
   - **Balloon angioplasty** with or without stenting (especially in older patients).



Differences in Blood Pressure Between Arms: Summary

BP Difference	Associated Features	Clinical Interpretation
Up to 10 mmHg	None	**Normal variant** (physiological)
>10 mmHg (abnormal)	- Radio-radial or radio-femoral delay - **No leg claudication**	**Proximal coarctation of the aorta**
>10 mmHg (abnormal)	- Arm claudication - Intermittent vertigo, ataxia, diplopia - Facial sensory symptoms - **No leg claudication**	**Subclavian steal syndrome**
>10 mmHg (abnormal)	- **Leg claudication** (pain triggered by exercise, relieved by rest)	**Peripheral vascular disease**

Hypertension

Definition

- **Essential Hypertension**: BP ≥140/90 mmHg with no secondary cause identified.
- **Secondary Hypertension**: BP elevation due to an identifiable underlying condition.

Causes

1. **Essential Hypertension** (95% of cases): Multifactorial (genetic and environmental factors).
2. **Secondary Hypertension** (5% of cases):
   - Renal: Renal artery stenosis, glomerulonephritis.
   - Endocrine: Cushing syndrome, hyperthyroidism, Conn syndrome.
   - Coarctation of the aorta.
   - Estrogen: Use of oral contraceptives.
   - Neurological: Raised intracranial pressure, psychostimulants.
   - Treatment-related: Glucocorticoids, NSAIDs.

Diagnosis

- **NICE recommendation**: Use **Ambulatory Blood Pressure Monitoring (ABPM)** or **Home Blood Pressure Monitoring (HBPM)** to confirm diagnosis.
  - Clinic BP ≥ 140/90 mmHg + ABPM/HBPM average ≥ 135/85 mmHg.

Blood Pressure Measurement Guidelines

- Measure in **both arms**; if difference >15 mmHg, use higher reading.
- Use **ABPM** to prevent diagnosing **white-coat hypertension**.
- For **postural hypotension**, measure BP seated and standing.

Hypertension Stages

Stage	Criteria
Stage 1	Clinic BP ≥ 140/90 mmHg + ABPM/HBPM average ≥ 135/85 mmHg
Stage 2	Clinic BP ≥ 160/100 mmHg + ABPM/HBPM average ≥ 150/95 mmHg
Severe (Stage 3)	Clinic systolic BP ≥ 180 mmHg or diastolic BP ≥ 120 mmHg

Management

Non-Pharmacological

- **Weight loss**: 10 kg weight loss can reduce BP by 15-20 mmHg.
- **Salt reduction**: <6g/day reduces systolic BP by ~10 mmHg.
- **Smoking cessation** and **alcohol reduction**.

Pharmacological Management (Stepwise Approach)

Step	Patient Characteristics	Medication
Step 1	Age ≤ 55 or T2DM: **ACEi/ARB**	Black African: **CCB**
Step 2	Not controlled on monotherapy	Add **CCB** or **diuretic**
Step 3	Not controlled on dual therapy	Triple therapy (ACEi/ARB + CCB + diuretic)
Step 4	Resistant hypertension	Add **spironolactone**, or **beta/alpha-blocker**

Drug Choice for Specific Conditions

Condition	Preferred Drugs
Diabetes (with proteinuria)	ACE inhibitors or ARBs.
Heart failure/Angina	ACE inhibitors, beta-blockers, diuretics.
Chronic kidney disease	ACE inhibitors or ARBs (careful monitoring).
Pregnancy	Labetalol (1st line), Nifedipine (2nd line), Methyldopa (3rd line).
African/Caribbean patients	Calcium channel blockers (1st line).
Post-MI	Beta-blockers, ACE inhibitors.

Blood Pressure Targets

Age	Clinic BP Target	ABPM/HBPM Target
<80	<140/90 mmHg	<135/85 mmHg
>80	<150/90 mmHg	<145/85 mmHg

Malignant Hypertension (Accelerated Hypertension)

- **Definition**: BP ≥180/120 mmHg + retinal haemorrhage and/or papilloedema.
- **Hallmark: Fibrinoid necrosis** of arterioles, especially in kidneys.
- **Management**: As per **hypertensive emergency**.

Secondary Hypertension: Causes & Indicators

- **Primary Hyperaldosteronism** (Conn's syndrome): Most common secondary cause.
- **Renal Diseases**: Glomerulonephritis, renal artery stenosis.
- **Endocrine Disorders**: Phaeochromocytoma, Cushing's syndrome.
- **Coarctation of the Aorta**: Common non-renal cause.
- **Drug-induced**: NSAIDs, oral contraceptives.

Hypertension in Pregnancy

- **Pre-eclampsia**: BP >140/90 mmHg + proteinuria after 20 weeks.
- **Eclampsia**: Pre-eclampsia + seizures.
- **Risk Factors**: Nulliparity, multiple pregnancy, obesity, diabetes, family history.
- **Prevention**: Aspirin 75–150 mg daily from 12 weeks.
- **Treatment**:

Stage	Preferred Treatment
Pre-eclampsia	Labetalol (1st), Nifedipine (2nd), Methyldopa (3rd)
Eclampsia	**Magnesium sulphate** for seizure management

Hypertension terms (NICE guidelines)

Term	Definition
Hypertension	clinic BP of ≥140/90 mmHg or higher and ABPM daytime average or HBPM average of ≥135/85 mmHg.
White-coat hypertension	A discrepancy of more than 20/10 mmHg between clinic and average daytime ABPM or average HBPM measurements at the time of diagnosis.
Masked hypertension	Clinic BP measurements are normal (<140/90 mmHg), but higher when taken outside the clinic using average daytime ABPM or average HBPM BP measurements.
Persistent hypertension	High blood pressure at repeated clinical encounters.
severe hypertension	Stage 3 hypertension: Clinic systolic BP ≥ 180 mmHg or clinic diastolic BP ≥ 120 mmHg.
Accelerated hypertension (malignant hypertension)	A severe increase in BP to **≥180/120 mmHg** (and often over 220/120 mmHg) **with signs of retinal haemorrhage and/or papilloedema** (swelling of the optic nerve). It is usually associated with new or progressive target organ damage and is also known as malignant hypertension.

The use of multiple anti-hypertensives at low doses is preferable to having fewer tablets at higher doses, given the synergistic effectiveness of targeting several mechanisms of hypertension.

MAP = diastolic blood pressure + [(systolic blood pressure - diastolic blood pressure)/3]
Or MAP = (2x diastolic + systolic)/3

Parenteral drugs for the treatment of hypertensive emergencies

	Side effects (SE)	Notes
Labetalol (Adrenergic inhibitor) Beta-Blocker With Alpha-Blocking Activity	Nausea/vomiting, paresthesias (e.g., scalp tingling), bronchospasm, dizziness, nausea, heart block	Avoid in acute decompensated heart failure. Use cautiously in obstructive or reactive airways. Beta-blockers should not be withdrawn abruptly but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.
Nitroglycerin (glyceryl trinitrate) (Vasodilators)	Hypoxemia, tachycardia (reflex sympathetic activation), headache, vomiting, flushing, methemoglobinemia, tolerance with prolonged use	used as adjunctive therapy for patients with acute coronary syndrome or acute pulmonary oedema. Contraindicated in patients with increased intracranial pressure (e.g., intracranial haemorrhage)

	Side effects (SE)	Notes
Nicardipine (Vasodilators) Calcium Channel Blocker, Dihydropyridine	Tachycardia, headache, dizziness, nausea, flushing, local phlebitis, oedema	Avoid use in acute heart failure. Caution with coronary ischemia.
Clevidipine (Vasodilators) Calcium Channel Blocker, Dihydropyridine	Atrial fibrillation (most common SE), nausea, lipid formulation contains potential allergens (eg, soy, egg)	Avoid in patients with defective lipid metabolism (hypertriglyceridemia is an expected SE). Patients who develop hypertriglyceridemia (e.g., >500 mg/dL) are at risk of developing pancreatitis. Dihydropyridine calcium channel blockers may cause negative inotropic effects and exacerbate HF.
Hydralazine (Vasodilators) Direct vasodilation of arterioles	Sudden precipitous drop in blood pressure, tachycardia, flushing, headache, vomiting, aggravation of angina	In general, hydralazine should be avoided due to its prolonged and unpredictable hypotensive effect. Contraindicated in coronary artery disease, mitral valve rheumatic heart disease, and SLE.
Nitroprusside (Vasodilators)	Elevated intracranial pressure, decreased cerebral blood flow, reduced coronary blood flow in CAD, cyanide and thiocyanate toxicity, nausea, vomiting, muscle spasm, flushing, sweating.	In general, nitroprusside should be avoided due to its toxicity. avoid in AMI, CAD, CVA, elevated intracranial pressure, renal or hepatic impairment.
Phentolamine (Adrenergic inhibitor) Alpha $_1$ Blocker	Tachycardia, flushing, headache, nausea/vomiting	An alternative option for catecholamine excess (e.g., adrenergic crisis secondary to pheochromocytoma or cocaine overdose).

Comparison of Hypertensive Emergency and Urgency

Parameter	Hypertensive Urgency	Hypertensive Emergency
Definition	BP ≥ 180/120 mmHg **without target organ damage.**	BP ≥ 180/120 mmHg **with acute target organ damage** (e.g., stroke, MI, aortic dissection, pulmonary oedema).
Clinical Features	Usually asymptomatic or mild symptoms like headache, dizziness.	Symptoms of organ dysfunction: chest pain, dyspnoea, altered mental status, neurological deficits.

Parameter	Hypertensive Urgency	Hypertensive Emergency
Management	**Oral antihypertensive therapy** to gradually lower BP over 24-48 hours.	**Immediate IV antihypertensive therapy** (e.g., labetalol, nitroprusside) to reduce BP promptly.
Goal of BP Reduction	Gradual reduction to < 160/100 mmHg over 24-48 hours.	Controlled BP reduction (e.g., reduce MAP by 20-25% within the first hour).
Monitoring	Outpatient management with **regular follow-up.**	Requires **continuous BP monitoring** in an intensive care setting.

Secondary hypertension

Different diagnostics for causes of secondary hypertension	
Diagnostic findings	**Underlying condition**
▪ Hypokalaemia	▪ Conn syndrome ▪ Renal artery stenosis
▪ Metabolic alkalosis and ↑ aldosterone-to-renin ratio	▪ Conn syndrome
▪ Difference in blood pressure in **both** arms	▪ Takayasu arteritis ▪ Aortic dissection ▪ Aortic arch syndrome ▪ Subclavian steal syndrome
▪ Of **upper** and **lower** limbs	▪ Coarctation of the aorta distal to the left subclavian artery
▪ Daytime sleepiness (Epworth scale, Berlin questionnaire) ▪ Nondipping in 24-hour blood pressure monitoring (the failure of BP to fall by ≥10% during sleep.)	▪ Obstructive sleep apnoea
▪ Increased 24-hour urinary metanephrines	▪ Pheochromocytoma
▪ ↑ Serum calcium, ↑ PTH level, ↓ serum phosphates	▪ Hyperparathyroidism
▪ ↑ Serum cortisol	▪ Excess of glucocorticoids (e.g., Cushing syndrome)
▪ ↓TSH, ↑ free T4	▪ Hyperthyroidism

Differences in blood pressure between arms:

- **Up to 10 mmHg difference →** Normal variant (physiological)
- **Difference > 10 mmHg: →** abnormal:
  - ⇨ **+ radio-radial or radio-femoral delay (NO Leg claudication) →** proximal coarctation **of the aorta (involves the left subclavian artery origin)**
  - ⇨ **+ arm claudication, intermittent vertigo, ataxia or diplopia, or facial sensory symptoms (NO Leg claudication) → Subclavian steal syndrome**
  - ⇨ **+ Leg claudication (chronic intermittent leg pain, exacerbated by exercise and relieved by rest) →** **Peripheral vascular disease**

Hypertension in pregnancy

Pre-existing hypertension	Pregnancy-induced hypertension (PIH, also known as gestational hypertension)	Pre-eclampsia
A history of hypertension before pregnancy or BP > 140/90 mmHg before 20 weeks gestation	Hypertension (as defined above) occurring in the second half of pregnancy (i.e. after 20 weeks)	Pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours)
No proteinuria, no oedema	No proteinuria, no oedema	Oedema may occur but is now less commonly used as a criterion
Occurs in 3-5% of pregnancies and is more common in older women	Occurs in around 5-7% of pregnancies	Occurs in around 5% of pregnancies
	Resolves following birth (typically after one month). Women with PIH are at increased risk of future pre-eclampsia or hypertension later in life	

Treatment of hypertension in the postnatal period (NICE guidelines June 2019)
• **If women not planning to breastfeed → treat as hypertension in general**
• **If women planning to breastfeed:** ⇨ 1st line: ▪ **non-black African or Caribbean women: enalapril** ▪ **black African or Caribbean women: nifedipine or amlodipine if the woman has previously used this to successfully control her BP.** ⇨ 2nd line: **combination of nifedipine (or amlodipine) and enalapril** ⇨ 3rd line: **add atenolol or labetalol to the combination treatment or swapping 1 of the medicines already being used for atenolol or labetalol.**
• **Avoid using diuretics or angiotensin receptor blockers for women who are breastfeeding.**

Pulmonary arterial hypertension (PAH)

Definition

- PAH is a subtype of pulmonary hypertension characterized by increased pressure in the pulmonary arteries due to narrowing or obstruction in the small pulmonary arterioles.
- **Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg** at rest measured via **right heart catheterization** with **pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg**.

Causes / Classification (WHO Classification)

1. **Group 1: PAH** (Primary cause)
    - Idiopathic
    - Heritable (e.g., BMPR2 gene mutation)
    - Associated with conditions like **connective tissue diseases** (e.g., scleroderma), **HIV infection, portal hypertension**, and **congenital heart diseases**.
    - Drug/toxin-induced (e.g., appetite suppressants).
2. **Group 2**: PH due to left heart disease.
3. **Group 3**: PH due to lung disease or hypoxia (e.g., COPD, ILD).
4. **Group 4**: Chronic thromboembolic pulmonary hypertension (CTEPH).
5. **Group 5**: PH with unclear/multifactorial mechanisms (e.g., hematologic or metabolic disorders).

Clinical Features

- **Early Symptoms**:
    - Dyspnoea on exertion.
    - Fatigue.
    - Chest pain.
    - Syncope (due to low cardiac output).
- **Late Symptoms**:
    - Peripheral oedema (right heart failure).
    - Cyanosis.
    - Raised jugular venous pressure (JVP).
    - Hepatomegaly (due to right heart strain).

Diagnosis

- **Initial Investigations**:
    - **Echocardiography**: Screening tool to estimate pulmonary artery pressures.
    - **ECG**: Right ventricular hypertrophy, right axis deviation, and right atrial enlargement.
    - **Chest X-ray**: Enlarged pulmonary arteries and right heart enlargement.
    - **Pulmonary Function Tests (PFTs)**: Rule out lung diseases causing PH.
- **Confirmatory Investigation**:
    - **Right heart catheterization**: Gold standard for diagnosis to measure mPAP and PCWP.
- **Additional Tests**:
    - **V/Q scan**: Rule out CTEPH.
    - **Autoimmune screening**: Assess for connective tissue diseases.
    - **HIV and liver function tests**: Assess for related diseases.

Management

1. **General Measures**:
    - **Oxygen therapy**: For hypoxic patients.
    - **Diuretics**: Manage fluid overload from right heart failure.

- o **Anticoagulation**: In selected cases (e.g., CTEPH).

2. **Targeted Pharmacologic Therapy**:
   - o **Endothelin Receptor Antagonists (ERA)**:
     - Examples: Bosentan, Ambrisentan.
     - Reduce pulmonary vascular resistance.
   - o **Phosphodiesterase-5 Inhibitors (PDE-5 inhibitors)**:
     - Examples: Sildenafil, Tadalafil.
     - Improve pulmonary vasodilation.
   - o **Prostacyclin Analogues / Receptor Agonists**:
     - Examples: Epoprostenol, Treprostinil, Selexipag.
     - Potent vasodilators.
   - o **Soluble Guanylate Cyclase (sGC) Stimulators**:
     - Example: Riociguat.
     - Enhance NO signalling and vasodilation.
3. **Advanced Treatments**:
   - o **Balloon Atrial Septostomy**: Decompress the right heart in severe cases.
   - o **Lung Transplantation**: Considered for refractory PAH despite medical treatment.

Complications

- Right ventricular failure.
- Arrhythmias (e.g., atrial fibrillation).
- Sudden cardiac death.

World Health Organization (WHO) functional classification for pulmonary hypertension

Class	WHO functional classification for pulmonary hypertension
I	No limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.
II	Slight limitation of physical activity. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope. Comfortable at rest.
III	Marked limitation of physical activity. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope. Comfortable at rest
IV	Inability to carry on any physical activity without symptoms. Dyspnea and/or fatigue may be present even at rest.

Valvular lesions

Mitral stenosis (MS)

Pathophysiology

- Mechanical obstruction of blood flow to the left ventricle (LV) → ↓ diastolic filling, ↓ stroke volume, ↓ cardiac output (forward heart failure).
- ↑ Left atrial pressure → pulmonary hypertension, cardiogenic pulmonary edema, right ventricular hypertrophy (backward heart failure).

Causes

- **Common**: Rheumatic fever (worsens during pregnancy).
- **Rare**: Calcification of mitral valve, autoimmune diseases (SLE, rheumatoid arthritis), congenital causes, mucopolysaccharidoses, carcinoid.

Clinical Features

- **General Signs**: Malar flush, dyspnea, low-volume pulse, tapping apex beat.
- **Auscultation**: Loud S1, mid-late diastolic murmur with pre-systolic accentuation, best heard at the apex in expiration.
- **Opening Snap**: Early diastolic sound suggesting mobile mitral valve; disappears with heavy calcification.

Complications

- **Atrial Compression**: Dysphagia, hoarseness (Ortner syndrome).
- **Atrial Fibrillation**: Embolic events (e.g., stroke), acute heart failure.
- **Right Heart Failure**: Orthopnea, paroxysmal nocturnal dyspnea (PND), edema, hemoptysis.

Investigations

- **Transthoracic Echocardiography (TTE)**: Assess mitral valve area (≤1.5 cm² = severe MS), RV/LA enlargement, pulmonary hypertension.
- **Chest X-ray**: Left atrial enlargement (double density sign), cardiomegaly, pulmonary congestion.
- **ECG**: Atrial fibrillation, left atrial enlargement (P mitrale), right ventricular hypertrophy.

Management

- **Asymptomatic MS**: Regular echocardiographic follow-up.
  - Every 3–5 years if MVA >1.5 cm²
  - Annually if MVA <1.0 cm²
- **Symptomatic Severe MS**:
  - **1st line**: Transcatheter valvotomy if valve morphology is favorable.
  - **2nd line**: Surgical valve replacement if valvotomy is unsuitable.
- **Indications for Surgery**: Unfavorable anatomy, thrombus in the left atrium, or mixed valvular disease.

MS in Pregnancy

- **Overview**: Poorly tolerated due to increased cardiac output in pregnancy, often becoming symptomatic in the second trimester.
- **Management**:
  - Mild symptoms: Beta-blockers or diuretics.
  - Severe MS: Percutaneous mitral balloon valvuloplasty if symptoms persist.
  - **Delivery**: Vaginal delivery preferred; C-section only for obstetric reasons.

Mitral regurgitation (MR)

Causes

- Myxomatous degeneration **(the most common cause of MR in UK).**
- **Left atrial enlargement → mitral regurgitation by affecting posterior leaflet** (anterior leaflet is not affected, because of its attachment to the root of the aorta).
- Papillary muscle rupture (cardiac complication seen 3-14 days post-myocardial infarction)
- MR associated with Marfan syndrome and Ehlers-Danlos syndrome.

Features

- Symptoms: dyspnoea, usually on exertion → decreased exercise tolerance. Palpitations.
- Signs: soft S1, split S2. Pan-systolic murmur (a holosystolic blowing murmur at the apex, radiating to axilla), **intensified by** isometric exercise and thus helps to differentiate it from other systolic murmurs. Sudden standing and amyl nitrite **decrease** the murmur.

Feature suggests more severe MR: left ventricle enlargement, and the **apex beat displacement**, and a **systolic thrill**.

Diagnosis: Transthoracic echo is the diagnostic test of choice

Management

- **Asymptomatic chronic MR:**
  - ⇨ Left ventricular ejection fraction >60% and/or left ventricular end-systolic diameter <45 mm → ACE inhibitors + beta-blockers
  - ⇨ Left ventricular ejection fraction ≤60% and/or left ventricular end-systolic diameter ≥45 mm → surgery
- **Symptomatic chronic MR**
  - ⇨ Left ventricular ejection fraction ≥30% → surgery + medical treatment (ACE inhibitors, beta-blockers, and diuretics.)
  - ⇨ Left ventricular ejection fraction <30% → medical treatment

Mitral valve prolapse (MVP)

Epidemiology

- common, occurring in around 5-10 % of the population.
- the most common valvular defect in the United States
- more common in females.

Causes

- usually idiopathic
- inherited in an autosomal dominant fashion.

Features

- atypical chest pain (the most common symptom)
- palpitations
- dyspnea, exercise intolerance,
- dizziness or syncope,
- panic and anxiety disorders.
- mid-systolic click (occurs later if patient squatting)
- late systolic murmur (longer if patient standing) heard best at the apex

Complications

- mitral regurgitation,
- arrhythmias (including long QT),
- emboli,
- sudden death

Treatment

- Mild to moderate mitral regurgitation
  - ⇨ follow-up in clinic with repeat echocardiograms to monitor progression.
- Mitral valve replacement is only indicated in:
  - ⇨ severe mitral regurgitation or
  - ⇨ if there are signs of concomitant LV compromise (reduced ejection fraction or new dilatation of the LV).
- If a surgical mitral valve replacement are indicated, coronary angiogram should be part of the pre-op work-up for potential concomitant coronary artery bypass grafting.

Aortic regurgitation (AR)

Causes

- **Due to valve disease**
  - ⇨ bicuspid aortic valve
    - **the most common cause of chronic AR in a young patient is a congenital bicuspid valve.**
    - Bicuspid valve is also a common cause of early-onset aortic stenosis.
  - ⇨ infective endocarditis
    - the vegetations prevent the valve from creating a proper seal to prevent backflow during diastole.
  - ⇨ rheumatic fever
  - ⇨ connective tissue diseases e.g. RA/SLE
- **Due to aortic root disease**
  - ⇨ aortic dissection
  - ⇨ Spondyloarthropathies (e.g. **ankylosing spondylitis**)
    - Ankylosing spondylitis is strongly associated with aortic regurgitation (occurs in 4% of cases).
    - An aortitis leads to aortic root dilatation with subsequent failure of leaflet coaptation.
  - ⇨ hypertension
  - ⇨ syphilis
  - ⇨ Marfan's,
  - ⇨ Ehler-Danlos syndrome

Causes of acute aortic regurgitation:

- ascending aortic dissection,
- infective endocarditis,
- collagen vascular disorders such as Marfan's
- trauma,
- dehiscence of a prosthetic valve.

Features

- early diastolic murmur
  - ⇨ heard along the left sternal border
  - ⇨ heard best while the patient is leaning forward on deep expiration.
- collapsing pulse
- wide pulse pressure
- mid-diastolic Austin-Flint murmur
  - ⇨ **It is a low-frequency mid/late diastolic murmur**
  - ⇨ due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams.
  - ⇨ There is no correlation between the presence of murmur and severity of AR, or aetiology.
- Note that there is often an aortic systolic flow murmur because there is an increased volume of blood in the LV due to the regurgitation.
- **Isolated LV dilatation (other chambers are normal) on ECHO due to volume overload**
  - ⇨ (AS, HOCM & ↑ BP → hypertrophy and a smaller LV cavity)
- Pulsus bisferiens; increased pulse pressure; visible, forceful, and bounding peripheral pulses (water hammer)
- Corrigan's pulse - visible and vigorous arterial pulsations in neck
- **Musset's sign - Bobbing of the head,** due to the arterial pulsations in the neck
- Quincke's sign - Capillary pulsations of the nail bed
- Muller's sign - Pulsations of the uvula
- Traube's sign - Loud systolic sound over femoral arteries ('pistol-shot' femorals)
- Duroziez sign - diastolic murmur proximal to femoral artery compression (due to flow reversal).
- Hill's sign (Higher systolic in leg than arm)

Signs of severity of AR

- Soft S2
- S3
- characteristic of the murmur. (Duration and loudness) (cf with AS)
  - ⇨ As the lesion becomes **more severe,** the murmur shortens.
- Apex beat displaced and thrusting
- CCF (pulmonary oedema)
- Wide pulse pressure
- collapsing pulse,
- Hill's sign (Higher systolic in leg than arm)

Investigations

- **Echocardiogram** (the most important test)
  - ⇨ **Echocardiographic markers of severe AR**
    - Width of AR jet on colour flow > 65 % of LVOT
    - regurgitant fraction (RF) > 50 %
    - left ventricular end-diastolic diameter (LVEDD) > 70mm
    - left ventricular end-systolic diameter (LVESD) > 50mm
- Cardiac catheterisation
  - ⇨ may be performed if there is doubt over the severity of the regurgitation;
  - ⇨ severity is estimated by the degree of contrast that fills the ventricles after injection into the aortic root.

Treatment

- **Asymptomatic:**
  - ⇨ Asymptomatic without signs of sever AR:
    - **ACEI improve the prognosis in asymptomatic left ventricular dysfunction.**
    - Beta blockers **should be avoided** as these prolong diastole and therefore would increase the regurgitant fraction.
  - ⇨ Asymptomatic with signs of sever AR: surgery (**Indications for surgery in asymptomatic**):
    - signs of sever AR (echo criteria):
      - ❖ **LV ejection fraction under 55%**
      - ❖ LV end diastolic diameter greater than 7 cm
      - ❖ LV end systolic diameter greater than 5 cm.
  - ⇨ Patient has moderate AR and is undergoing coronary artery bypass surgery or other surgery involving the ascending aorta = surgery
- **Symptomatic**: Surgical
  - ⇨ Symptomatic (CCF, angina)
  - ⇨ deteriorating exercise tolerance, or
  - ⇨ abnormal hemodynamic responses to exercise, such as inability to augment blood pressure during a treadmill study

Aortic stenosis (AS)

Epidemiology: AS is the most common valve problem in the UK.

Risk factors

- Age >60 years
- Congenitally bicuspid aortic valve
- Rheumatic heart disease
- **Chronic kidney disease**

Causes

- Degenerative calcification (tricuspid aortic valve calcification)
  - ⇨ The most common cause in older patients > 65 years
- **Congenital bicuspid aortic valve (BAV)**
  - ⇨ most common cause in younger patients < 65 years
- William's syndrome (supravalvular aortic stenosis)
- Post-rheumatic disease → fibrosis → Commissural fusion on ECHO
- Subvalvular: HOCM

Features

- **Symptoms**
  - ⇨ heart failure
  - ⇨ **SAD**
    - **S**yncope (40%)
    - **A**ngina or chest pain (50%)
    - **D**yspnea (60%): Exertional dyspnea is the most common initial complaint

- **Physical exam**
  - ⇨ pulse
    - narrow pulse pressure
    - slow rising pulse
    - pulsus parvus et tardus
      - weak pulses with a delayed peak
  - ⇨ **Displaced apex beat**
  - ⇨ thrill
  - ⇨ ejection systolic murmur (ESM): crescendo-decrescendo murmur, typically, a mid-systolic ejection murmur, radiates to carotid arteries (left often louder than right). Radiate to the right neck, decreases with standing, Valsalva, or handgrip.
  - ⇨ S4 heart sound from stiff or hypertrophic ventricle
  - ⇨ **S2 (Character of S2):** soft/absent S2, paradoxical splitting of S2

Associated conditions

- hemolytic anemia
- predisposes to bleeding due to an acquired von Willebrand deficiency caused by turbulent flow across the stenotic valve.
- chronic gastrointestinal bleeding that is associated with angiodysplasia.

The severity of aortic stenosis

- **Definition:** a valve area of less than 1.0 cm^2.
- **Features of severe aortic stenosis**

Features of severe aortic stenosis

1. **Narrow pulse pressure**
2. **Slow rising pulse**
3. **Delayed (mid-systolic) ejection systolic murmur (ESM)**
4. **Soft/absent S2**
5. **S4**
6. **Thrill**
7. **Duration of murmur**
8. **Left ventricular hypertrophy or failure**

Investigations

- **Echocardiography** (most important test): Key markers of severe AR:
  - ⇨ Width of AR jet > 65% of LVOT
  - ⇨ Regurgitant fraction > 50%
  - ⇨ LVEDD > 70 mm
  - ⇨ LVESD > 50 mm
- **Cardiac Catheterisation**: Used when severity of AR is uncertain.

Management

- **Symptomatic patient** → surgical aortic valve replacement. If not fit for aortic valve replacement → Transcatheter aortic valve implantation (TAVI)
- **Asymptomatic patient with severe stenosis (transvalvular gradient > 50 mmHg, valve area <1 cm^2) but has an ejection faction of less than 50% → aortic valve replacement or TAVI if unsuitable.**

- **Asymptomatic patient** with severe stenosis but has an ejection fraction is greater than 50% → Exercise testing, If pass exercise testing →reviewed in six months.
- echo follow-up
- Patients undergoing open surgical valve replacement should first undergo coronary angiography to exclude any coronary stenosis that could simultaneously be treated with bypass grafting.

Heyde's syndrome

- **Association between microcytic anaemia and calcific aortic stenosis.**
- Heyde syndrome refers to a **triad of**
  1. aortic stenosis,
  2. acquired coagulopathy (von Willebrand syndrome type 2A) and
  3. anaemia due to bleeding from intestinal angiodysplasia or from an idiopathic site.
     - Angiodysplasia most commonly occur in the ascending colon, particularly the **caecum**.
- **Pathophysiology**
  - ⇨ destruction of von Willebrand's factor as the platelets traverse the stenosed valve resulting in bleeding per rectum.
- **Investigation**
  - ⇨ The investigation of choice after valve replacement is mesenteric angiography as the bleeding vessels are poorly visualised on colonoscopy.
    - This would look for the presence of angiodysplasia, which may be associated with aortic stenosis.
  - ⇨ All patients with aortic stenosis should be screened for iron deficiency anaemia.
- **Treatment**
  - ⇨ replace the valve
  - ⇨ Resection of the diseased bowel has also been described as a treatment.
- There is an association with jaundice and aortic stenosis; this is thought to be due to microangiopathic haemolysis.

Bicuspid aortic valve

Definition: fusion of two of the three aortic-valve leaflets in utero

Epidemiology

- most common form of congenital heart disease in adults (1-2% of population).
- predominantly affects males (2:1)

Genetics

- Bicuspid aortic valve tends to be sporadic although there is a reported familial incidence of approximately 9%.
- The European Society of Cardiology states that there is an estimated 10% chance of a first degree relative being affected
- NOTCH1 gene mutations may be responsible.

Associated conditions

- Left dominant coronary circulation (the posterior descending artery arises from the circumflex instead of the right coronary artery)
- Turner's syndrome
- Coarctation of the aorta (around 5% of patients)

Features

- Usually asymptomatic in childhood
- **Early systolic ejection click (the cardinal sign):** best heard at the apex

Complications

- The majority eventually develop aortic stenosis or regurgitation
- Higher risk for aortic dilation (most commonly involving the ascending aorta) and aortic dissection when the aorta is dilated.

Investigations

- Transthoracic echocardiography
- The ascending aorta in bicuspid aortic valve disease should be completely visualized by echocardiogram (and cardiovascular magnetic resonance imaging [CMR] or computed tomography [CT] if necessary) to evaluate for associated aortopathy.

Management

- **Aortic valve replacement is eventually likely to be required** (Only 15% of patients with a bicuspid aortic valve will have a normally functioning valve in the fifth decade, and this often continues to deteriorate with age).
- **Patient Instructions about endocarditis prophylaxis**

Tricuspid regurgitation

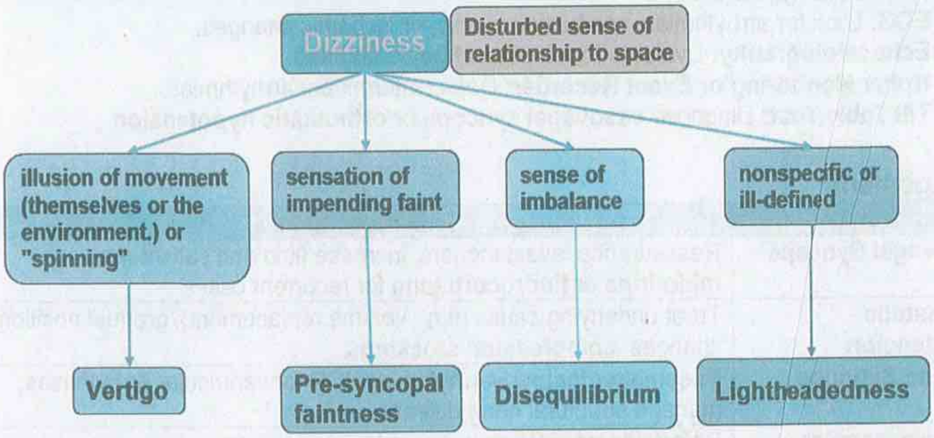
Causes

- pulmonary hypertension e.g. COPD (The most common cause)
- right ventricular dilation
- rheumatic heart disease
- infective endocarditis (especially intravenous drug users)
- **Ebstein's anomaly**
- carcinoid syndrome

Signs

- pan-systolic murmur
- giant V waves in JVP
- pulsatile hepatomegaly
- left parasternal heave

Arrhythmias



Syncope

Definition

- Syncope is a **sudden, transient loss of consciousness** due to **global cerebral hypoperfusion**, followed by spontaneous recovery.

Types and Causes of Syncope

Type	Mechanism	Examples
Reflex (Neurally Mediated) Syncope	Abnormal autonomic reflex causing vasodilation or bradycardia	**Vasovagal** (stress, pain), **Situational** (cough, urination)
Orthostatic Hypotension	Insufficient vascular tone upon standing	Volume depletion (dehydration, blood loss), autonomic dysfunction (e.g., Parkinson's, diabetes)
Cardiac Syncope	Arrhythmias or structural heart disease	**Arrhythmias** (VT, AV block), **Structural** (aortic stenosis, HOCM, PE)
Cerebrovascular Syncope	Rare, transient ischemia in brainstem	Vertebrobasilar insufficiency, subclavian steal syndrome

Clinical Features

- **Pre-syncope Symptoms:** Dizziness, light-headedness, nausea, blurred vision, palpitations.
- **Post-syncope Symptoms:** Fatigue, confusion, or none (quick recovery typical).
- **Triggers:** Stress, standing, exercise, dehydration, cough, or urination.
- **Duration:** Brief (seconds to minutes) with spontaneous recovery.
- **Warning Signs of High-Risk Syncope:** Occurs during exertion, associated chest pain, palpitations, family history of sudden death.

Approach to Diagnosis

1. **History and Physical Examination:**
   - Identify triggers, duration, and associated symptoms.
   - Assess for **cardiac** or **neurological** history.
2. **Vital Signs and Orthostatic Test:** Measure **blood pressure** lying, sitting, and standing (orthostatic hypotension).
3. **ECG:** Look for arrhythmias, conduction blocks, or ischemic changes.
4. **Echocardiography:** Evaluate for **structural heart disease**.
5. **Holter Monitoring or Event Recorder:** Detect intermittent arrhythmias.
6. **Tilt Table Test:** Diagnose **vasovagal syncope** or **orthostatic hypotension**.

Management

Type	Management
Vasovagal Syncope	Reassurance, avoid triggers, increase fluid and salt intake, **midodrine** or **fludrocortisone** for recurrent cases
Orthostatic Hypotension	Treat underlying cause (e.g., volume replacement), gradual position changes, **compression stockings**
Cardiac Syncope	**Pacemaker** for bradyarrhythmias, **ICD** for ventricular arrhythmias, manage structural heart disease
Cerebrovascular Syncope	Referral to **neurology** or **vascular surgery** if needed

Red Flags Requiring Urgent Evaluation

- Syncope during **exertion**.
- Associated with **chest pain** or **palpitations**.
- Family history of **sudden cardiac death**.
- **Severe injury** during syncope (e.g., head trauma).

Key Points

- **Vasovagal syncope** is the most common and benign form.
- **Cardiac syncope** is life-threatening and requires urgent evaluation.
- **Tilt table test** and **ECG monitoring** are essential for diagnosis.
- Management depends on the **underlying cause** and prevention of recurrences.

Emergency evaluation of syncope

- **Associated by headache with migrainoid features → Migraine**
- **Associated with post-ictal state, incontinence or prolonged LOC → seizure or CNS lesion**
- **Transient LOC**
  - ⇨ **A ssociated with exertion, chest pain or palpitation or family history of early cardiac or sudden death. Abnormal cardiac exam or ECG → Cardiac syncope from arrhythmia or structural heart disease**
  - ⇨ **Abnormal glucose → hypoglycaemia**
  - ⇨ **Abnormal haematocrit → anaemia**
  - ⇨ **Positive urine HCG → Pregnancy**
  - ⇨ **Orthostatic change and heart rate or BP or associated with assuming upright posture → orthostatic hypotension**

> ⇨ **Ingestion or toxic exposure → toxin related syncope**
> ⇨ **Abnormal respiratory pattern (immediately before to or during the event) → Hyperventilation or breath holding**
> ⇨ **Prodrome including dizziness, light-headedness, nausea, sweating, weakness or vision changes →vasovagal syncope**
> ⇨ **No clue → Conversion disorder**

Vertigo

Definition:

- Vertigo is a symptom of illusory (not real) movement, most commonly of spinning (turning around) of oneself or of the environment.

Pathophysiology:

- **Vertigo occurs due to asymmetry in the vestibular system caused by damage or dysfunction of the labyrinth, vestibular nerve, or central vestibular structures in the brainstem.**

Step-by-Step Approach to Vertigo

- Vertigo is a **sensation of spinning or dizziness** often related to disorders of the inner ear, central nervous system, or cardiovascular system. This step-by-step approach helps in **diagnosing and managing** the underlying cause.

Step 1: History Taking

1. **Characterize the Vertigo:**
   - **True vertigo** (spinning sensation) vs. **light-headedness** or **imbalance**.
2. **Duration and Frequency:**
   - **Seconds to minutes:** Benign Paroxysmal Positional Vertigo (BPPV)
   - **Minutes to hours:** Meniere's disease
   - **Hours to days:** Vestibular neuritis or labyrinthitis
3. **Triggers:**
   - **Head movement-related:** BPPV
   - **Stress, diet, or fatigue:** Meniere's disease
4. **Associated Symptoms:**
   - **Hearing loss or tinnitus:** Meniere's disease or labyrinthitis
   - **Neurological signs:** Suspect central vertigo (stroke, multiple sclerosis).
5. **Drug History:**
   - Ototoxic medications (e.g., aminoglycosides, loop diuretics).

Step 2: Physical Examination

1. **General Examination:** Blood pressure and heart rate (rule out hypotension).
2. **Ear Examination:** Assess for infection, wax impaction, or tympanic membrane abnormalities.
3. **Neurological Examination:**
   - Cranial nerve examination.
   - Look for **nystagmus** (involuntary eye movement).
   - Test for **ataxia** or other cerebellar signs.
4. **Dix-Hallpike Maneuver:** Positive test: Reproduces vertigo with nystagmus → **BPPV**.
5. **Head Impulse Test:** Corrective saccade suggests **vestibular neuritis**.

Step 3: Differentiating Peripheral vs. Central Vertigo

Feature	Peripheral Vertigo	Central Vertigo
Onset	Sudden	Gradual
Duration	Intermittent, short	Persistent or progressive
Nystagmus	Unidirectional, fatigues	Bidirectional or vertical, non-fatiguing
Associated Symptoms	Hearing loss, tinnitus	Neurological symptoms (e.g., diplopia)
Causes	BPPV, Meniere's disease, vestibular neuritis	Stroke, multiple sclerosis, tumors

Step 4: Diagnostic Tests

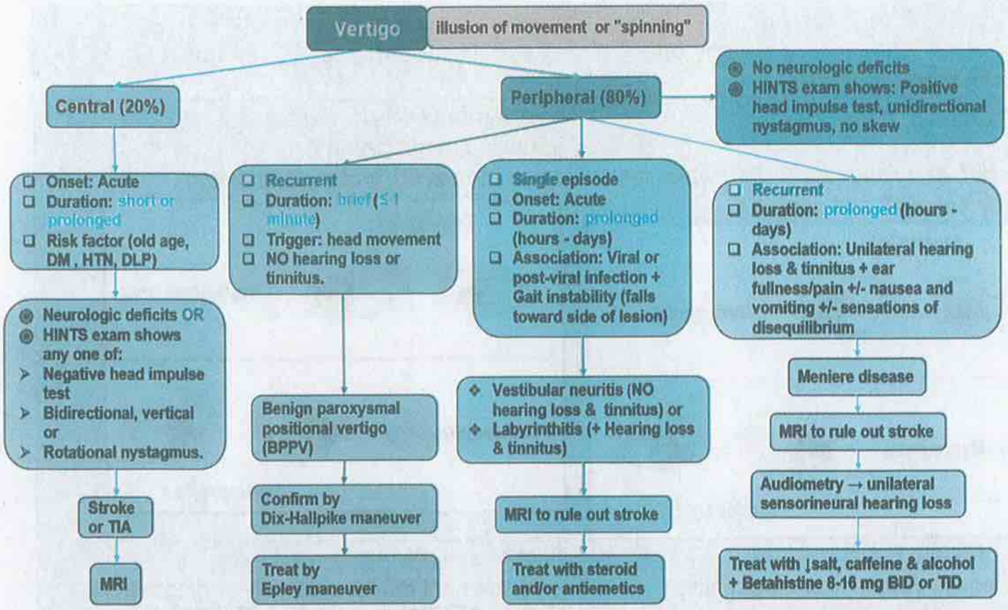
1. **Audiometry:** Assess for hearing loss (Meniere's disease, labyrinthitis).
2. **MRI/CT Brain:** Rule out stroke or central lesions in persistent vertigo with neurological signs.
3. **Blood Tests:** Evaluate for infections, electrolyte imbalances, or anemia.

Step 5: Management

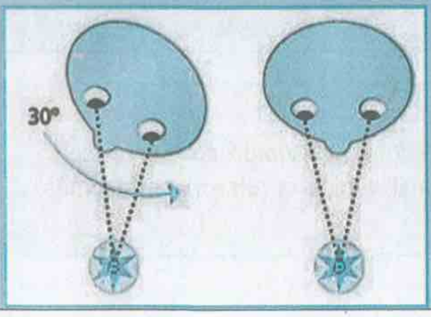
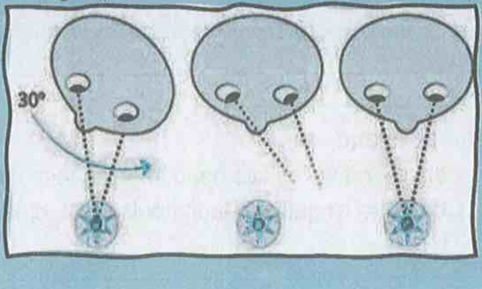
Condition	Management
BPPV	Epley maneuver, avoid rapid head movements
Meniere's Disease	Low salt diet, diuretics, betahistine
Vestibular Neuritis/Labyrinthitis	Corticosteroids, vestibular rehabilitation
Central Vertigo (e.g., stroke)	Urgent neurological referral, stroke management
Anxiety-related Vertigo	CBT, SSRIs, relaxation techniques

Clinical features of central versus peripheral vertigo

	Peripheral	Central
Nystagmus Direction	**Unidirectional**, fast component toward the normal ear; never reverses direction	Sometimes reverses direction when patient looks in the direction of slow component
Nystagmus Type	**Horizontal** with a torsional component, never purely torsional or vertical	Can be any direction
Nystagmus Effect of visual fixation	**Suppressed**	Not suppressed
Other neurologic signs	Absent	Often present
Postural instability	Unidirectional instability, **walking preserved**	Severe instability, patient often falls when walking
Deafness or tinnitus	May be present	Absent



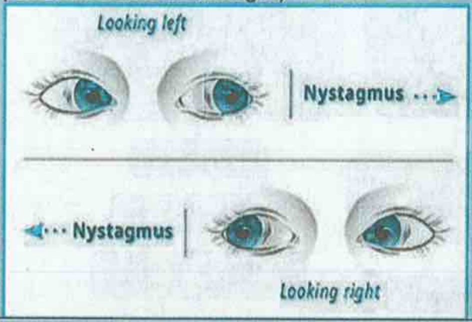
Interpretation of HINTS examination (Central vs Peripheral dysfunction)

Central vestibular dysfunction (eg, brain stem or cerebellar stroke): any one feature suggest central	Peripheral vestibular dysfunction (eg, vestibular neuritis or labyrinthitis)
Focal neurological finding: Present (Absence does not rule out central origin)	Focal neurological finding: Absent
Head Impulse Test (HI): Normal Eyes are able to remain fixed on target despite head movement (vestibulo-ocular reflex is intact)  	Head Impulse Test (HI): Abnormal Head movement causes the eyes to move off target followed by a rapid jerky movement back to target (vestibulo-ocular reflex is affected) 

<table>
<tr>
<th>Central vestibular dysfunction (eg, brain stem or cerebellar stroke): any one feature suggest central</th>
<th>Peripheral vestibular dysfunction (eg, vestibular neuritis or labyrinthitis)</th>
</tr>
<tr>
<td>

Nystagmus (N): Direction changing nystagmus

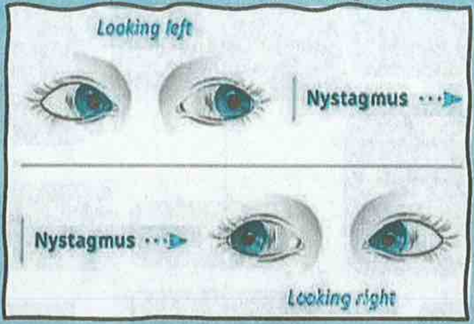
(direction of nystagmus differs when the patient looks left and right)



</td>
<td>

Nystagmus (N): Uni-directional nystagmus

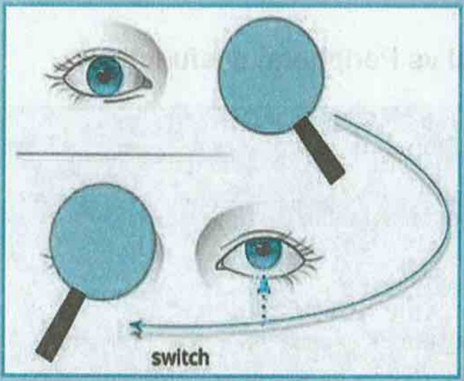
(direction of nystagmus remains the same when the patient looks left and right)



</td>
</tr>
<tr>
<td>

Test of skew (TS): Skew deviation

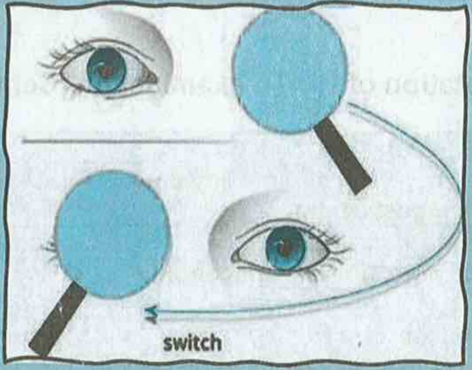
(eye moves vertically or diagonally)



</td>
<td>

Test of skew (TS): Absent skew

(eye does not moves vertically or diagonally)



</td>
</tr>
</table>

The HINTS exam:

- **Peripheral** = Positive head impulse test, unidirectional nystagmus, no skew
- **Central** = Negative head impulse test, bidirectional, vertical or rotational nystagmus.

Supraventricular tachycardia (SVT)

Definition

- Supraventricular tachycardia (SVT) refers to a group of **rapid heart rhythms** originating from **above the ventricles** (atria or AV node), typically with a heart rate of **>150 bpm**.

Types of SVT

Type	Mechanism	ECG Findings	Examples
Atrioventricular Nodal Reentrant Tachycardia (AVNRT)	Reentry circuit within the **AV node**	Narrow QRS, regular rhythm	Most common type of SVT
Atrioventricular Reentrant Tachycardia (AVRT)	Reentry circuit using an **accessory pathway**	Narrow QRS (can be wide if pre-excitation)	Includes **WPW syndrome**
Atrial Tachycardia	Ectopic focus from **atria** (not sinus node)	Abnormal P waves before each QRS	Multifocal atrial tachycardia (MAT)
Atrial Flutter	Reentry circuit within **atria**	Saw-tooth **flutter waves**, atrial rate ~300 bpm	Often converts to AF

Causes and Risk Factors

- **Electrolyte Imbalances** (e.g., hypokalemia, hypomagnesemia)
- **Stress or Anxiety**
- **Caffeine, Alcohol, Nicotine**
- **Structural heart disease** (e.g., heart failure, valvular disease)
- **Hyperthyroidism**

Clinical Features

- **Palpitations** (rapid heartbeats)
- **Dizziness** or **lightheadedness**
- **Dyspnoea**
- **Chest pain** (in patients with ischemic heart disease)
- **Syncope** (in rare cases)

ECG Findings

- **Narrow QRS complex** (<120 ms)
- **Regular rhythm** with a heart rate >150 bpm
- **P waves** may be absent or retrograde (in AVNRT)
- **QRS alternation** may occur with AVRT

Management

Situation	Treatment
Acute, Unstable SVT	**Immediate synchronized cardioversion** (50-100 J)
Acute, Stable SVT	**Vagal maneuvers** (e.g., carotid massage)
	IV Adenosine (6 mg, followed by 12 mg if ineffective)
	IV Beta-blockers or **calcium channel blockers** (e.g., verapamil, diltiazem)
Long-term management	**Beta-blockers** or **calcium channel blockers** for prevention
	Catheter ablation for recurrent SVT
WPW-related SVT	Avoid **AV nodal blockers** (e.g., beta-blockers, verapamil) due to risk of accessory pathway conduction

Complications
- **Hypotension** or **syncope** (in unstable cases)
- **Heart failure** (in chronic or poorly controlled SVT)
- **Tachycardia-induced cardiomyopathy**
- **Atrial fibrillation or flutter**

Key Points
- **Adenosine** is the drug of choice for acute termination of stable SVT.
- **Vagal maneuvers** are effective in terminating AVNRT.
- **Catheter ablation** offers a curative option for recurrent SVT.
- In **WPW syndrome**, avoid AV nodal blockers to prevent dangerous arrhythmias.

Premature ventricular ectopic (PVEs)
Definition
- Premature ventricular ectopics (PVEs), also known as **premature ventricular contractions (PVCs)**, are **early heartbeats originating from the ventricles**, disrupting the regular heart rhythm.

Causes and Risk Factors
- **Electrolyte imbalances:** Hypokalemia, hypomagnesemia
- **Cardiac conditions:** Ischemic heart disease, heart failure, myocarditis
- **Stimulants:** Caffeine, alcohol, nicotine
- **Medications:** Digitalis toxicity, sympathomimetics
- **Stress and anxiety**

Clinical Features
- **Asymptomatic** (most common)
- **Palpitations** or skipped beats
- **Dizziness** or light-headedness (rare)
- **Fatigue**
- Worsening symptoms in structural heart disease or with frequent PVCs

ECG Findings
- **Wide QRS complex** occurring earlier than expected
- **No preceding P wave** (ventricular origin)
- **Compensatory pause** after the ectopic beat
- PVCs may appear as **isolated, bigeminy, or trigeminy** patterns.

Complications
- May trigger **ventricular tachycardia** or **ventricular fibrillation** in patients with structural heart disease.
- **Tachycardia-induced cardiomyopathy** with frequent PVCs (>10% of total beats).

Management
1. **Lifestyle Modification:**
   - Avoid caffeine, alcohol, and nicotine.
   - Manage stress and anxiety.
2. **Medical Management:**
   - **Beta-blockers** (e.g., metoprolol) for symptomatic PVCs.
   - **Calcium channel blockers** in some cases.
   - **Antiarrhythmics** (e.g., amiodarone) for refractory PVCs in patients with structural heart disease.

3. **Catheter Ablation:**
   - Considered for **frequent PVCs** causing symptoms or ventricular dysfunction.
4. **Monitor and Manage Underlying Conditions:**
   - Treat ischemic heart disease or electrolyte imbalances.

Key Points

- PVEs are often **benign** and asymptomatic but may require treatment if symptomatic or frequent.
- **Beta-blockers** are the first-line therapy for symptomatic cases.
- **Catheter ablation** is an option for refractory or frequent PVEs.

Arrhythmogenic right ventricular cardiomyopathy(ARVC)

Definition

- ARVC is a **genetic cardiomyopathy** characterized by the progressive replacement of **right ventricular myocardium with fibrofatty tissue**, predisposing to **ventricular arrhythmias** and **sudden cardiac death (SCD)**, particularly in young individuals and athletes.

Causes and Pathophysiology

- **Genetic mutations** in **desmosomal proteins** (e.g., plakophilin, desmoglein, desmoplakin).
- **Autosomal dominant inheritance** with variable penetrance.
- Progressive replacement of myocardial tissue with **fat and fibrous tissue**, leading to **arrhythmias** and **ventricular dysfunction**.

Clinical Features

- **Palpitations**
- **Syncope** (particularly during exercise)
- **Sudden cardiac death** (especially in athletes)
- **Right-sided heart failure** in advanced cases

ECG Findings

- **T-wave inversions** in V1-V3 (right precordial leads)
- **Epsilon waves**: Small positive deflections at the end of QRS in V1-V3
- **Ventricular tachycardia** with **left bundle branch block (LBBB)** morphology

Diagnosis

- **ECG abnormalities** and history of arrhythmia or syncope.
- **Echocardiography:** Right ventricular dilation and dysfunction.
- **Cardiac MRI:** Identifies fibrofatty replacement of myocardium.
- **Genetic testing** for desmosomal mutations.
- **Endomyocardial biopsy** (rarely used).

Management

1. **Lifestyle Modification:**
   - **Avoid strenuous exercise** to reduce the risk of arrhythmias and sudden death.
2. **Medical Management:**
   - **Beta-blockers** to control arrhythmias.
   - **Antiarrhythmics** (e.g., sotalol, amiodarone) for recurrent arrhythmias.
3. **Implantable Cardioverter-Defibrillator (ICD):**
   - For patients with a history of **sustained ventricular tachycardia** or **sudden cardiac arrest**.
   - **Primary prevention** in high-risk patients.

4. **Catheter Ablation:**
    - For refractory ventricular tachycardia.
5. **Heart Transplant:**
    - Considered for end-stage heart failure.

Complications

- **Sudden cardiac death** (especially in athletes)
- **Heart failure** (right ventricular failure)
- **Progressive biventricular dysfunction** in advanced stages

Key Points

- ARVC is a **genetic disorder** leading to **ventricular arrhythmias** and **sudden death**, especially in **young athletes**.
- **Beta-blockers and ICDs** are the mainstay of management.
- **Exercise restriction** is essential to prevent arrhythmia-related events.
- **Cardiac MRI** is crucial for diagnosis by identifying **fibrofatty replacement** in the right ventricle.

Atrial fibrillation (AF)

Definition

- Atrial fibrillation (AF) is a **supraventricular arrhythmia** characterized by **disorganized atrial electrical activity** leading to **irregularly irregular ventricular response** and loss of coordinated atrial contraction.

Types of AF

1. **Paroxysmal AF:** Episodes last <7 days, self-terminating.
2. **Persistent AF:** Lasts >7 days, requires intervention to terminate.
3. **Long-standing Persistent AF:** Continuous AF >12 months.
4. **Permanent AF:** Cannot or will not be restored to sinus rhythm.

Causes and Risk Factors

- **Cardiac:** Hypertension, coronary artery disease, heart failure, valvular disease (mitral stenosis).
- **Non-cardiac:** Hyperthyroidism, COPD, alcohol use ("holiday heart"), obesity, electrolyte disturbances.
- **Age and Genetics:** More common in older adults.

Clinical Features

- **Palpitations**
- **Fatigue** and **dyspnea**
- **Dizziness** or **light-headedness**
- **Syncope** (rare)
- **Stroke or thromboembolism** due to stasis of blood in atria.

ECG Findings

- **Irregularly irregular rhythm**.
- **Absent P waves**, replaced by **fibrillatory waves**.
- **Variable RR intervals**.
- **Narrow QRS complex** unless a bundle branch block is present.

Complications

- **Stroke** and **systemic embolism** (due to thrombus formation in the left atrium).
- **Heart failure** (due to loss of atrial contribution to ventricular filling).
- **Tachycardia-induced cardiomyopathy** from prolonged rapid heart rates.

Management

1. **Rate Control:**
   - **Beta-blockers** (e.g., metoprolol).
   - **Calcium channel blockers** (e.g., diltiazem, verapamil).
   - **Digoxin** (in heart failure).
2. **Rhythm Control:**
   - **Antiarrhythmics:** Amiodarone, flecainide, sotalol.
   - **Electrical cardioversion** if rhythm restoration is needed urgently.
   - **Catheter ablation** for refractory or recurrent AF.
3. **Anticoagulation:**
   - **CHA_2DS_2-VASc score** to assess stroke risk.
   - **DOACs** (e.g., apixaban, rivaroxaban) or **warfarin** for stroke prevention.
4. **Lifestyle Modifications:**
   - Manage hypertension, weight loss, reduce alcohol intake.

Key Points

- AF increases the risk of **stroke** and **heart failure.**
- Management includes **rate or rhythm control** and **anticoagulation** to prevent embolism.
- Stroke risk is assessed using the **CHA_2DS_2-VASc score**, guiding anticoagulation.

Assess stroke risk by using the **CHA_2DS_2-VASc** score

	Risk factor	Points
C	Congestive heart failure	1
H	Hypertension (or treated hypertension)	1
A_2	Age ≥ 75 years	2
	Age 65-74 years	1
D	Diabetes	1
S_2	Prior Stroke or TIA	2
V	Vascular disease (including ischaemic heart disease and peripheral arterial disease)	1
S	Sex (female)	1

⇨ **Suggested anticoagulation strategy based on the score:**

Score	Anticoagulation
0	No treatment
1	Males: Consider anticoagulation Females: No treatment (this is because their score of 1 is only reached due to their gender)
≥ 2	Offer anticoagulation

- ⇨ **Indications of anticoagulation regardless CHADS2-VASc score: valvular heart disease,** prior peripheral embolism, and intracardiac thrombus.
- ⇨ **Assess bleeding risk (when considering anticoagulation)** by using the **ORBIT** bleeding risk score (recommended by nice as the best tool , now replaced the HAS-BLED score)

Risk Factor For Bleeding	Points Attributed
Age ≥ 75 years	1 point
Haemoglobin (<13 mg/dL in men and <12 mg/dL in women), haematocrit (<40% in men and <36% in women) or history of anaemia	2 points
Bleeding history	2 points
eGFR < 60 mg/dL/1.73 m2	1 point
Treatment with an antiplatelet agent	1 point

☞ **Interpretation:**

ORBIT Score	Risk group	Bleeds per 100 patient-years
0-2	Low	2.4
3	Medium	4.7
4-7	High	8.1

Atrial flutter

Definition

- Rapid, regular atrial depolarizations at a characteristic rate of approximately 300 beats/min and a regular ventricular rate of about 150 beats/min
- Usually caused by a single macroreentrant rhythm within the atria.

Causes & Comorbidity

- Atrial flutter is unusual in patients without heart disease (valvular heart disease, cardiomyopathy, post-cardiac surgery, pericardial disease, prior heart surgery)
- Frequently coexists with atrial fibrillation
- Acute or chronic pulmonary diseases.

Epidemiology

- Sex: ♂ > ♀ (5:2)
- Risk of atrial flutter increases with age

Features

- **Similar to atrial fibrillation (palpitations, fatigue, lightheadedness, and mild shortness of breath)**
- **Most patients are asymptomatic**
- **Tachycardia with a regular pulse (regularly irregular if atrial flutter occurs with a variable AV block occurring in a fixed pattern (2:1 or 4:1)**

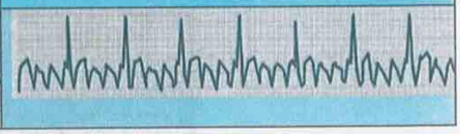
ECG findings

- Regular, narrow QRS complexes
- flutter waves, which are a **saw-tooth pattern** of atrial activation, **most prominent in inferior leads (II, III, aVF)**
- Atrial rate is often around 300/min

- Ventricular or heart rate depends on the block. For example if there is 2:1 block the ventricular rate will be 150/min
- Flutter waves may be visible following carotid sinus massage or adenosine

Management: similar to atrial fibrillation

Atrial fibrillation VS Atrial flutter

	Atrial fibrillation	Atrial flutter
Prevalence	More common	Less common
Origin	roots of the pulmonary veins	Begins in the right atrium
Symptoms	More symptoms	Mild symptoms
Pulse	Fast, irregular pulse	Fast, regular pulse
P wave	Invisible	Visible (saw-tooth pattern) , rate around 300/min with 2 -4 waves for every QRS
QRS (heart rate)	Variable	Most commonly 150 bpm (2:1)
Rate-control	Possible and preferred for most patient	Difficult , so rhythm control is preferred
Cardioversion	Less sensitive	More sensitive
Risk of systemic embolism	More	Less
ECG		

Multifocal atrial tachycardia (MAT)

Definition

- Multifocal atrial tachycardia (MAT) is a **supraventricular arrhythmia** characterized by the presence of **multiple atrial foci**, leading to irregular tachycardia with **at least three distinct P-wave morphologies** on ECG.

Causes and Risk Factors

- **Pulmonary diseases:** Chronic obstructive pulmonary disease (COPD) is the most common cause.
- **Electrolyte imbalances:** Hypokalemia, hypomagnesemia.
- **Acute illness:** Sepsis, heart failure.
- **Medications:** Theophylline, beta-agonists.
- **Underlying cardiac conditions:** Coronary artery disease, valvular heart disease.

Clinical Features

- **Palpitations**
- **Dyspnea** (often associated with underlying pulmonary disease)
- **Fatigue**
- May present with symptoms of **worsening respiratory or cardiac condition**.

ECG Findings

- **Irregular rhythm** with a heart rate >100 bpm.
- **At least three different P-wave morphologies.**
- **Varying PR intervals.**
- **Isoelectric baseline** between P waves (distinguishing it from atrial fibrillation).

Management

1. **Treat Underlying Cause:**
   - Manage pulmonary disease (e.g., COPD exacerbation).
   - Correct electrolyte imbalances (potassium, magnesium).
   - Adjust or stop medications that may trigger MAT.
2. **Rate Control:**
   - **Calcium channel blockers** (e.g., verapamil, diltiazem) – First-line.
   - **Beta-blockers** (used cautiously in pulmonary disease).
3. **Rhythm Control:**
   - Usually not required, as restoring the underlying condition resolves MAT.

Prognosis

- Good prognosis if the **underlying cause** is managed effectively.
- MAT often resolves with treatment of **acute pulmonary or metabolic conditions**.

Key Points

- MAT is common in **COPD patients** and is triggered by multiple atrial foci.
- **ECG hallmark:** Irregular rhythm with at least **three distinct P-wave morphologies**.
- Management focuses on **treating the underlying cause** and using **calcium channel blockers** for rate control.

Multifocal atrial tachycardia has ≥ 3 P-wave morphologies on ECG

Atrial myxoma

Definition

- Atrial myxoma is a **benign primary cardiac tumour**, most commonly found in the **left atrium.** It can obstruct blood flow and cause embolic or constitutional symptoms.

Epidemiology

- **Most common primary cardiac tumour** (approximately 75% of cases).
- **More frequent in females** and adults aged 30-60 years.
- Most often located in the **left atrium** (80% of cases), near the fossa ovalis.

Pathophysiology

- Tumour grows on a stalk attached to the atrial septum.
- Can obstruct the **mitral valve**, leading to heart failure symptoms.
- Fragments may **embolize**, causing systemic embolism.

Clinical Features

1. **Cardiac Symptoms:**
   - Dyspnoea, orthopnoea (mimics mitral valve disease)
   - Palpitations
   - Syncope (from valve obstruction)
2. **Embolic Symptoms:**
   - Stroke or transient ischaemic attack (TIA)
   - Peripheral embolism
3. **Constitutional Symptoms:**
   - Fever, weight loss, fatigue
   - Arthralgia
   - Symptoms due to the release of **inflammatory cytokines**

Diagnosis

- **Echocardiography:**
  - **Transesophageal echocardiography (TEE)** provides better visualization.
- **ECG:** May show atrial fibrillation or conduction abnormalities.
- **CT or MRI:** Used if further imaging is needed for diagnosis.

Complications

- **Mitral valve obstruction:** Mimics mitral stenosis, leading to heart failure.
- **Embolization:** Stroke, TIA, or peripheral embolism.
- **Sudden death:** Rare, but can occur if obstruction is severe.

Management

- **Surgical excision** is the treatment of choice.
- **Follow-up echocardiography** to monitor for recurrence.
- Manage any complications such as embolism with anticoagulation if indicated.

Prognosis

- Good prognosis with **complete surgical resection**.
- Recurrence is rare but can occur, especially in familial cases.

Key Points

- Atrial myxoma is the **most common primary cardiac tumour,** typically found in the **left atrium.**
- It presents with a triad of **cardiac, embolic, and constitutional symptoms**.
- **Echocardiography** is the diagnostic tool of choice, and **surgical resection** is curative.

Heart block

Definition

- Heart block refers to a disruption in the **electrical conduction** system of the heart, specifically involving delayed or blocked transmission between the **atria and ventricles**.

Types of Heart Block

1. **First-Degree Heart Block**
   - **Description:** Prolonged PR interval (>200 ms) without missed beats.
   - **ECG Finding:** Consistently prolonged PR interval.
   - **Symptoms:** Usually asymptomatic.
   - **Management:** No treatment required; monitor periodically.
2. **Second-Degree Heart Block**
   - **Mobitz Type I (Wenckebach):**
     - Gradual prolongation of the PR interval until a beat is dropped.

    - **Symptoms:** May cause dizziness or syncope.
    - **Management:** Monitor, treat if symptomatic (e.g., with pacemaker).
  - **Mobitz Type II:**
    - Intermittently dropped QRS complexes **without PR prolongation**.
    - **Risk:** High risk of progression to complete heart block.
    - **Management: Pacemaker implantation** recommended.

3. **Third-Degree (Complete) Heart Block**
   - **Description:** No communication between the atria and ventricles (complete AV dissociation).
   - **ECG Finding:** P waves and QRS complexes occur independently.
   - **Symptoms:** Severe bradycardia, syncope, fatigue, and heart failure.
   - **Management: Immediate pacemaker** implantation required.

Causes

- **Ischemic heart disease** (e.g., MI)
- **Degenerative disease** (e.g., fibrosis, Lev's disease)
- **Medications** (e.g., beta-blockers, calcium channel blockers, digoxin)
- **Electrolyte imbalances** (e.g., hyperkalemia)
- **Congenital heart block** (e.g., in newborns of mothers with autoimmune diseases)

Clinical Features

- Dizziness or light-headedness
- Syncope
- Fatigue
- **Bradycardia**
- In severe cases: **heart failure** or sudden cardiac arrest

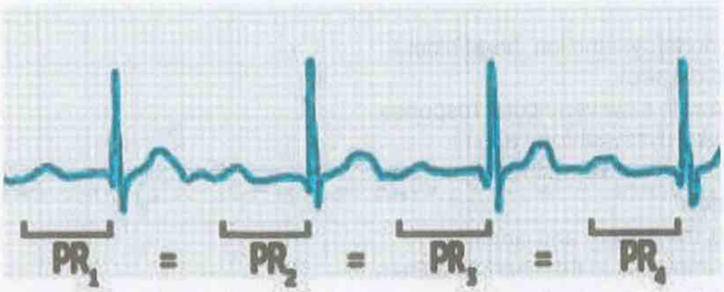
Management Overview

1. **First-Degree Heart Block:**
   - No treatment required; monitor periodically.
2. **Second-Degree Mobitz I:**
   - Monitor; pacemaker if symptomatic.
3. **Second-Degree Mobitz II and Complete Heart Block:**
   - **Permanent pacemaker implantation** is required.

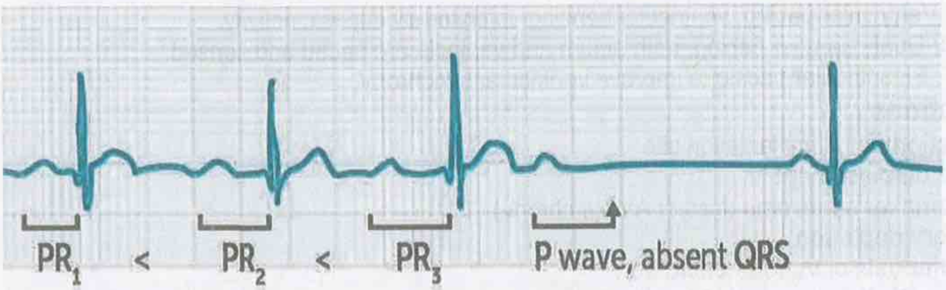
Key Points

- **Mobitz II** and **complete heart block** are serious conditions requiring **pacemaker implantation**.
- **First-degree heart block** is typically benign.
- **Regular monitoring** is essential for early detection of progression in partial heart block cases.

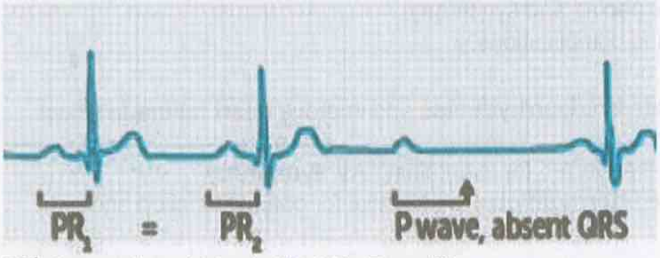
Mobitz type II block can progress to third-degree heart block; therefore, all patients should be admitted for continuous cardiac monitoring and treatment.



1st degree heart block



2nd degree heart block (Mobitz type I, Wenckebach)



2nd degree heart block (Mobitz Type II)

Pacemakers

Definition

- A **pacemaker** is a device implanted to regulate heart rhythm by delivering electrical impulses to stimulate the heart when intrinsic electrical activity is insufficient or absent.

Types of Pacemakers

1. **Single-Chamber Pacemaker:**
   - Stimulates either the **right atrium** or **right ventricle**.
   - Used for **sinus node dysfunction** or **chronic atrial fibrillation** with bradycardia.
2. **Dual-Chamber Pacemaker:**
   - Stimulates both the **right atrium** and **right ventricle**, maintaining **AV synchrony**.
   - Used in **AV block** or **sinus node dysfunction**.
3. **Biventricular Pacemaker (Cardiac Resynchronization Therapy, CRT):**
   - Stimulates both **ventricles** to improve coordination.
   - Used in **heart failure** with ventricular dyssynchrony.

Indications
- **Bradycardia** (e.g., sinus node dysfunction, heart block)
- **AV block** (second or third degree)
- **Chronic atrial fibrillation** with slow ventricular response
- **Heart failure** with ventricular dyssynchrony (CRT)
- **Neurocardiogenic syncope** or **carotid sinus syndrome**

Components of a Pacemaker
- **Pulse Generator:** Houses the battery and circuitry.
- **Leads:** Wires that deliver impulses to the heart chambers.
- **Electrodes:** Stimulate the heart muscle directly.

Modes of Pacing (Common Modes)
- **VVI:** Ventricular pacing, ventricular sensing, inhibited by intrinsic activity.
- **DDD:** Dual-chamber pacing, both atrium and ventricle are paced and sensed.
- **CRT:** Biventricular pacing to improve ventricular synchrony.

Complications
- **Infection** at the implantation site
- **Lead displacement**
- **Pacemaker syndrome** (loss of AV synchrony)
- **Battery depletion**
- **Thrombosis** or **venous occlusion**

Pacemaker Follow-up and Monitoring
- **Regular pacemaker interrogation** to assess battery life and pacing parameters.
- Adjust settings to ensure proper pacing and synchrony.
- Monitor for **lead malfunction** and complications.

Key Points
- Pacemakers are used to **regulate bradyarrhythmias** and improve **heart failure** in select cases.
- **Dual-chamber pacemakers** are preferred for maintaining **AV synchrony**.
- **Regular follow-ups** and **device interrogation** are essential for optimal function and complication management.

Pacemaker syndrome

Definition
- Pacemaker syndrome refers to the occurrence of **unpleasant symptoms** due to the **loss of synchrony** between atrial and ventricular contractions in patients with pacemakers, particularly **single-chamber ventricular pacemakers.**

Causes
- Loss of **AV synchrony** (ventricle pacing without proper atrial contribution)
- **Retrograde conduction** of ventricular impulses into the atria
- Inappropriate **ventricular pacing rate**

Clinical Features
- **Fatigue**
- **Dizziness** or **light-headedness**
- **Palpitations**
- **Hypotension**
- **Syncope**
- **Congestive heart failure** symptoms (e.g., dyspnoea, oedema)

Diagnosis

- **Clinical symptoms** occurring after pacemaker implantation
- **ECG** showing loss of AV synchrony
- **Pacemaker interrogation** to evaluate pacing patterns
- **Echocardiography** to assess cardiac output and AV dyssynchrony

Management

1. **Reprogramming the Pacemaker:**
   - Switch from **ventricular-only pacing** (VVI mode) to **dual-chamber pacing** (DDD mode) to restore AV synchrony.
   - Adjust pacing rate if inappropriate.
2. **Upgrading the Pacemaker:**
   - Consider switching to a **dual-chamber or biventricular pacemaker** if reprogramming fails.
3. **Pharmacological Support:**
   - Beta-blockers or other rate-controlling drugs to optimize heart rate and rhythm.

Prevention

- Prefer **dual-chamber pacemakers** during implantation to maintain AV synchrony.
- Optimize pacemaker settings through **regular follow-up and interrogation**.

Key Points

- **Pacemaker syndrome** occurs due to **AV dyssynchrony** in patients with pacemakers, leading to symptoms like **fatigue, syncope, and heart failure**.
- **Switching to dual-chamber pacing** is the primary solution to restore synchrony.
- Regular **pacemaker follow-ups** are essential to prevent and detect pacemaker syndrome.

Pacemaker syndrome
• **Loss of AV synchrony.** • **Retrograde VA conduction.** • **Absence of rate response to physiological need.**

Brugada syndrome

Definition

- Brugada syndrome is a **genetic arrhythmogenic disorder** associated with an increased risk of **sudden cardiac death** due to ventricular fibrillation. It is characterized by **ST-segment elevation** in the right precordial leads (V1-V3) on ECG and occurs without structural heart disease.

Causes and Pathophysiology

- **Genetic mutation** in the **SCN5A** gene (affecting sodium channels)
- Results in **impaired sodium channel function**, leading to abnormal cardiac conduction.
- **Triggers:** Fever, medications (e.g., sodium channel blockers), electrolyte imbalances, or alcohol.

Clinical Features

- **Syncope**
- **Palpitations**
- **Seizures** (due to arrhythmias)
- **Sudden cardiac arrest**, especially during sleep or rest
- Family history of **sudden unexplained death**

ECG Findings

- **ST-segment elevation** in V1-V3
- **Right bundle branch block (RBBB)-like pattern**
- **Brugada Type 1 pattern:** Coved ST-segment elevation ≥2 mm followed by a negative T wave
- ECG abnormalities may be **intermittent** and can be unmasked by **fever** or **sodium channel blockers.**

Diagnosis

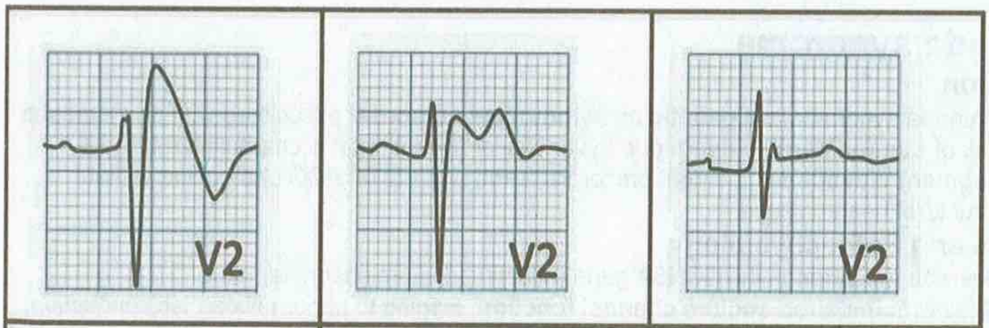
- **ECG** showing a characteristic Brugada pattern.
- **Drug challenge** with sodium channel blockers (e.g., ajmaline, flecainide) to unmask ECG changes.
- **Genetic testing** for **SCN5A** mutations.
- **Family screening** if a diagnosis is confirmed.

Management

1. **Acute Management of VT/VF:**
   - **Defibrillation** for ventricular fibrillation or cardiac arrest.
2. **Long-Term Management:**
   - **Implantable Cardioverter-Defibrillator (ICD):** For patients with a history of VT, VF, or sudden cardiac arrest.
   - **Lifestyle modifications:** Avoid fever and drugs that exacerbate Brugada syndrome.
   - **Quinidine:** In patients who are not ICD candidates or with frequent arrhythmias.

Key Points

- Brugada syndrome increases the risk of **sudden cardiac death**, especially in young males.
- ECG findings are **intermittent** and may be triggered by fever or medications.
- **ICD implantation** is the only effective treatment for preventing sudden cardiac death.
- **Family screening** is essential to identify asymptomatic carriers.



Type 1 ECG. Note 2mm coved ST elevation. This is the most diagnostic ECG type.	**Type 2 ECG (sometimes called saddleback). Note 2mm ST elevation with biphasic T wave. The lowest point in the wave is still 1mm above baseline.**	**Type 3 ECG shows ST elevation less than 2mm, not meeting criteria for Type 1 or 2.**

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Definition

- CPVT is a rare, **genetic arrhythmogenic disorder** characterized by **exercise- or stress-induced polymorphic ventricular tachycardia** (VT), which can lead to **syncope, cardiac arrest, or sudden death.**

Causes and Pathophysiology

- **Genetic mutations** affecting calcium-handling proteins:
  - **RYR2** (Ryanodine receptor gene) – Most common
  - **CASQ2** (Calsequestrin gene) – Less common
- **Mechanism:** Excessive intracellular calcium release during stress leads to ventricular arrhythmias.

Clinical Features

- **Exercise-induced palpitations**
- **Syncope** triggered by emotional or physical stress
- **Sudden cardiac arrest** (especially in young patients)
- **No structural heart disease** on imaging

ECG Findings

- **Normal ECG at rest**
- During exercise or stress:
  - **Polymorphic VT** or **bidirectional VT**
  - Episodes are not associated with QT prolongation.

Diagnosis

- **Exercise stress testing** or **Holter monitoring** to provoke arrhythmia.
- **Genetic testing** for mutations in **RYR2** or **CASQ2**.

Management

1. **Acute Management of VT Episodes:**
   - **Beta-blockers** (e.g., propranolol) to prevent episodes.
   - **IV magnesium** and **cardioversion** for unstable VT.
2. **Long-Term Management:**
   - **Beta-blockers** (first-line therapy): Reduce heart rate and suppress arrhythmias.
   - **Flecainide**: Add-on therapy to reduce arrhythmogenic calcium release.
   - **Lifestyle modifications:** Avoid strenuous exercise and emotional stress.
   - **Implantable Cardioverter-Defibrillator (ICD):** For high-risk patients with recurrent syncope or VT.

Key Points

- CPVT occurs **without structural heart disease** and presents with **stress- or exercise-induced VT**.
- **Beta-blockers** are the cornerstone of treatment.
- **ICD implantation** may be required in high-risk cases to prevent sudden cardiac death.
- Genetic screening is essential for diagnosis and family counseling.

Ventricular tachycardia (VT)

Definition

- Ventricular tachycardia (VT) is a **fast heart rhythm** originating from the **ventricles**, defined by a heart rate of >100 bpm, lasting ≥30 seconds (sustained) or <30 seconds (non-sustained).

Classification

1. **By Duration:**
   - **Sustained VT:** Lasts ≥30 seconds or requires intervention.
   - **Non-sustained VT:** Lasts <30 seconds, self-terminating.
2. **By QRS Morphology:**
   - **Monomorphic VT:** Regular QRS complexes of the same shape and duration.
   - **Polymorphic VT:** Varying QRS shapes (e.g., torsades de pointes).

Causes

- **Ischemic heart disease** (most common)
- **Cardiomyopathies** (e.g., dilated, hypertrophic)
- **Electrolyte abnormalities** (hypokalemia, hypomagnesemia)
- **Drug toxicity** (e.g., digoxin, antiarrhythmics)
- **Congenital syndromes** (e.g., Long QT syndrome, Brugada syndrome)

Clinical Features

- Palpitations
- Dizziness or syncope
- Chest pain
- Sudden cardiac arrest

ECG Findings

- **Wide QRS complexes** (>120 ms)
- **Rate >100 bpm**
- **Regular or irregular rhythm**
- **Atrioventricular dissociation** (P waves independent of QRS complexes)

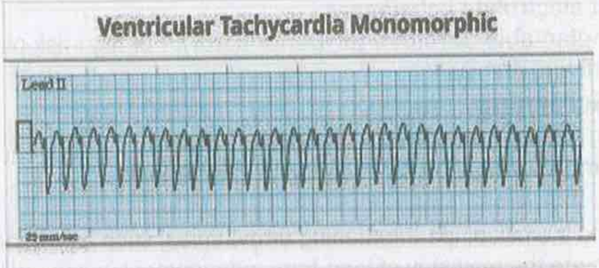
Management

1. **Acute Management:**
   - **Unstable VT:**
     - **Immediate synchronized DC cardioversion** (100-200 J)
   - **Stable VT:**
     - **IV antiarrhythmics**: Amiodarone (150 mg IV over 10 minutes), Procainamide, or Lidocaine
     - **Magnesium sulfate** for polymorphic VT (if associated with torsades de pointes)
2. **Long-Term Management:**
   - **Beta-blockers** (e.g., metoprolol, bisoprolol) for post-MI patients
   - **Amiodarone** for recurrent VT
   - **ICD (Implantable Cardioverter-Defibrillator):** For high-risk patients
   - **Catheter ablation**: For drug-refractory VT

Key Points

- **Synchronized cardioversion** is the treatment of choice for **unstable VT**.
- **Amiodarone** or **lidocaine** is preferred for stable VT.
- **ICD implantation** significantly reduces mortality in high-risk patients with recurrent or life-threatening VT.
- Close monitoring of electrolytes can prevent VT episodes in vulnerable patients.

	Unsynchronized	Synchronized
When to deliver electricity	At any point in cycle	Not during the T-wave
Indications	V-fib, pulseless VT	Everything except V-fib and pulseless VT



Long QT syndrome

Definition

- Long QT Syndrome (LQTS) characterized by **prolongation of the QT interval** on ECG, predisposing to **torsades de pointes (TdP)** and sudden cardiac death.

Causes

1. **Congenital LQTS:**
   - Genetic mutations affecting ion channels (e.g., **LQT1, LQT2, LQT3**)
2. **Acquired LQTS:**
   - **Medications:**
     - Antiarrhythmics (e.g., sotalol, amiodarone)
     - Antibiotics (e.g., macrolides, fluoroquinolones)
     - Antipsychotics (e.g., haloperidol)
     - Antidepressants (e.g., tricyclic antidepressants)
   - **Electrolyte Imbalance:**
     - Hypokalemia
     - Hypomagnesemia
     - Hypocalcemia

Clinical Features

- Palpitations
- Syncope
- Seizures (due to arrhythmias)
- Sudden cardiac arrest

ECG Findings

- **Prolonged QT interval:** (440 ms in men, 460 ms in women)
- **T-wave abnormalities** (broad, notched, or low amplitude)

Management

1. **Acute Management:**
   - If torsades de pointes occurs:
     - **IV Magnesium Sulfate**: 2 g IV over 10-15 minutes
     - **Cardioversion** for unstable patients

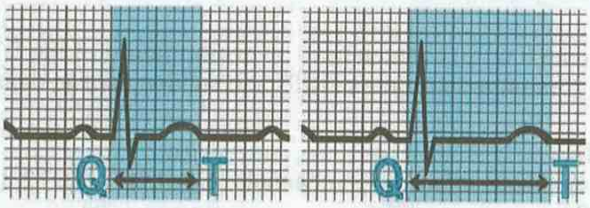
2. **Long-Term Management:**
    - **Beta-blockers** (e.g., propranolol, nadolol) – First-line treatment for congenital LQTS
    - **Lifestyle modifications**: Avoid triggers (e.g., strenuous exercise for LQT1)
    - **Discontinue QT-prolonging drugs**
    - **Correct electrolyte imbalances**
    - **ICD (Implantable Cardioverter-Defibrillator):** For high-risk patients or those with recurrent arrhythmias

Prevention and Screening

- Genetic testing for family members in congenital cases
- Regular **ECG monitoring** if on QT-prolonging medications

Key Points

- LQTS increases the risk of life-threatening arrhythmias, such as **torsades de pointes**.
- **Beta-blockers** are the mainstay of long-term management in congenital LQTS.
- Close monitoring and **discontinuation of QT-prolonging drugs** are essential in acquired LQTS.



Normal QT Interval   Long QT Interval

Torsades de pointes (TdP)

Definition

- Torsades de Pointes (TdP) is a specific type of **polymorphic ventricular tachycardia** associated with a prolonged **QT interval**, characterized by twisting QRS complexes around the isoelectric line on the ECG.

Causes

1. **Electrolyte Imbalance:**
    - Hypokalemia
    - Hypomagnesemia
    - Hypocalcemia
2. **Drugs that Prolong QT Interval:**
    - Antiarrhythmics (e.g., quinidine, sotalol)
    - Antibiotics (e.g., macrolides, fluoroquinolones)
    - Antipsychotics (e.g., haloperidol)
    - Antidepressants (e.g., tricyclic antidepressants)
3. **Congenital Long QT Syndrome**
4. **Bradycardia or AV block**

Clinical Features

- Palpitations
- Dizziness
- Syncope
- Sudden cardiac arrest

ECG Findings

- **Prolonged QT interval** (>440 ms in men, >460 ms in women)
- **Polymorphic QRS complexes** with a twisting pattern around the baseline

Management

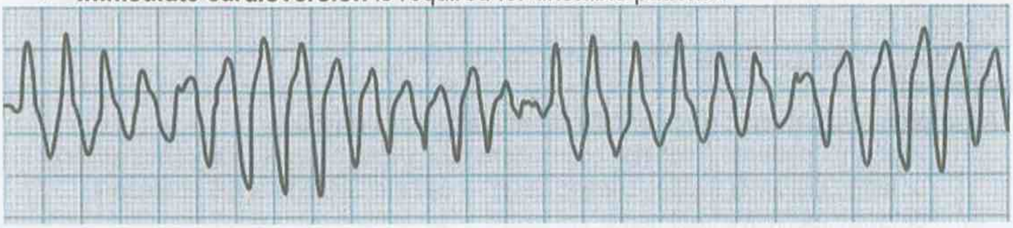
1. **Acute Management:**
   - **Unstable:** Immediate **DC cardioversion**
   - **Stable:**
     - **IV Magnesium Sulfate:** 2 g IV over 10-15 minutes
     - **Correct electrolyte imbalances** (e.g., potassium, magnesium)
     - **Stop QT-prolonging drugs**
2. **Refractory Cases:**
   - **Temporary pacing** to increase heart rate
   - **Isoproterenol infusion** for bradycardia-related TdP

Prevention

- Avoid QT-prolonging medications in high-risk individuals
- Monitor electrolytes in patients with cardiac disease
- Genetic screening in congenital cases

Key Points

- TdP is a life-threatening arrhythmia often triggered by **prolonged QT interval**.
- **IV magnesium** is the first-line treatment, even if serum magnesium levels are normal.
- **Immediate cardioversion** is required for unstable patients.



Torsades de Pointes

Wolff-Parkinson White (WPW)

Pathophysiology

- Due to a congenital accessory conduction pathway, called the **bundle of Kent**, that connects the atria to the ventricles, bypassing the AV node and leading to **ventricular preexcitation**. As the accessory pathway does not slow conduction, SVT and AF can degenerate rapidly to VF.

Types

- **Type A WPW:** Involves a left-sided accessory pathway and presents with positive delta waves in lead V1, often associated with more severe arrhythmias.
- **Type B WPW:** Involves a right-sided pathway with negative delta waves in V1, typically carrying a slightly lower arrhythmia risk.

Parameter	Type A WPW Syndrome	Type B WPW Syndrome
Accessory Pathway Location	Left-sided accessory pathway (usually in the left free wall)	Right-sided accessory pathway (often in the right free wall)
ECG Pattern	- Positive delta wave in V1 - **Wide QRS complex** with a predominantly **R wave** in precordial leads - **Left axis deviation** or normal	- Negative delta wave in V1 - **Wide QRS complex** with a predominantly **S wave** in V1 - **Right axis deviation**
Aetiology	Often associated with **structural heart abnormalities**	Often occurs without underlying structural heart disease
Prevalence	More common	Less common
Risk of Arrhythmia	Higher risk of atrial fibrillation and sudden cardiac death	Lower but still significant arrhythmia risk

Presentation

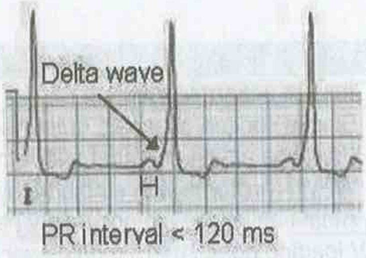
- **Most patients are asymptomatic.**
- **Palpitation:** most commonly SVT (often AV re-entrant tachycardia) can alternate with ventricular tachycardia (VT).
- **Worsening of SVT after using calcium blockers or digoxin**

Investigations

- **ECG:** Short PR interval, **delta wave** (a slurred upstroke at the start of the QRS complex), Widened QRS
- **Electrophysiologic studies (The most accurate test)**

Management

- **Asymptomatic patients: (incidentally found delta wave on ECG)**
  - **High-risk patients** (High-risk occupations e.g., pilots, athletes, school bus driver) or family history of sudden cardiac death → catheter ablation of the accessory pathway (definitive treatment)
  - **Low risk patients (no high risk features)→ Reassurance**
- **Symptomatic patients**
  - **Acute management**
    - **Unstable** (narrow or wide complex): BP <90/60 mmHg) → 50- to 360-J biphasic synchronised DC shock
    - **Stable narrow or wide-complex tachycardia → IV procainamide** (the most safest option) **or amiodarone.**
  - **Long term management**
    - **first-line:** catheter ablation (**definitive treatment** and the treatment of choice
    - **second line: Chronic medical therapy: flecainide, amiodarone, procainamide**
  - **Contraindicated drugs: ABCD drugs (Adenosine, B-Blockers, Calcium Channel Blockers, Digoxin** → blocking AV node →↑conduction rate through the accessory pathway, → ↑ventricular rate →↑ risk of ventricular fibrillation.



Antiarrhythmics: Vaughan Williams classification

Class	Examples	Mechanism of action
Ia	**Quinidine** **Procainamide** **Disopyramide**	1. Block sodium channels 2. Increases AP duration **Notes:** • Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia) • Procainamide may cause drug-induced lupus • **Disopyramide toxicity → Urinary retention**
Ib	**Lidocaine** **Mexiletine** **Tocainide**	1. Block sodium channels 2. Decreases AP duration
Ic	**Flecainide** **Encainide** **Propafenone**	1. Block sodium channels 2. No effect on AP duration
II	**Propranolol** **Atenolol** **Bisoprolol** **Metoprolol**	Beta-adrenoceptor antagonists
III	**Amiodarone** **Sotalol** **Ibutilide** **Bretylium**	Block potassium channels
IV	**Verapamil** **Diltiazem**	Calcium channel blockers

Procainamide

Parameter	Procainamide
Class	Class Ia antiarrhythmic
Mechanism of Action	- Blocks sodium channels (intermediate kinetics)
	- Prolongs action potential and refractory period
Primary Indications	- WPW syndrome with stable tachycardia - Atrial fibrillation with accessory pathway (WPW)
Administration	IV loading dose: 10-15 mg/kg over 20-30 min Maintenance infusion: 1-4 mg/min
Onset of Action	10-30 minutes (IV)
Half-Life	3-4 hours
Metabolism	Metabolized to NAPA (active metabolite)
Side Effects	- Hypotension, QRS prolongation, torsades de pointes - Lupus-like syndrome with long-term use
Contraindications	- QT prolongation, heart block without a pacemaker
Monitoring Requirements	Continuous ECG monitoring for QRS prolongation

Lidocaine

Parameter	Lidocaine
Class	Class Ib Antiarrhythmic
Mechanism of Action	Blocks sodium channels, shortens action potential and refractory period
Primary Indications	Ventricular tachycardia, ventricular fibrillation, post-MI arrhythmias
Administration	- IV Bolus: 1-1.5 mg/kg over 2-3 minutes - Repeat: 0.5-0.75 mg/kg every 5-10 minutes (max 3 mg/kg) - Maintenance: 1-4 mg/min
Onset and Duration	Rapid onset within minutes, half-life ~1.5-2 hours
Side Effects	CNS toxicity (e.g., seizures, confusion), hypotension, bradycardia
Contraindications	Severe liver disease, complete heart block without a pacemaker
Monitoring	ECG monitoring, assess for CNS symptoms
Use in WPW Syndrome	**Not effective** for WPW or supraventricular arrhythmias

Atropine

Attribute	Details
Class	Anticholinergic (Muscarinic receptor antagonist)
Mechanism of Action	- **Blocks muscarinic receptors** in the parasympathetic nervous system. - Increases heart rate by inhibiting vagal influence on the SA and AV nodes. - Reduces secretions and relaxes smooth muscle.
Indications	- **Bradycardia** (symptomatic or hemodynamically unstable) - **Asystole** or **PEA** with bradycardia component - **Antidote for organophosphate poisoning** - **Preoperative use** to reduce salivary and respiratory secretions
Dosing and Administration	- **Bradycardia**: 0.5 mg IV every 3–5 minutes (maximum dose: 3 mg) - **Asystole/PEA**: 1 mg IV (repeated as needed) - **Organophosphate poisoning**: 2 mg IV every 5–10 minutes until symptoms improve
Onset and Duration	- **Onset**: 1–2 minutes (IV) - **Duration**: 30–60 minutes
Side Effects	- **Cardiovascular**: Tachycardia, palpitations - **CNS**: Confusion, dizziness - **Gastrointestinal**: Dry mouth, constipation - **Urinary retention**
Contraindications	- **Tachycardia** or **arrhythmias** - **Narrow-angle glaucoma** - **Prostatic hypertrophy** (risk of urinary retention)
Monitoring	- Monitor **heart rate and ECG** during use. - Assess for **signs of anticholinergic toxicity** (confusion, blurred vision, dry mouth).
Drug Interactions	- Increased effects with **antihistamines**, **tricyclic antidepressants**, or **antipsychotics**.
Clinical Notes	- First-line drug for **symptomatic bradycardia** in Advanced Life Support (ALS) protocols. - Use cautiously in elderly patients due to risk of **confusion and urinary retention**. - If ineffective in bradycardia, consider **dopamine or epinephrine infusion**.

Adenosine

Attribute	Details
Class	Class V Antiarrhythmic (Miscellaneous)
Mechanism of Action	- **Activates adenosine receptors** in the AV node, causing **transient heart block** by inhibiting AV node conduction. - Hyperpolarizes the cell membrane, reducing automaticity and conduction.
Indications	- **Supraventricular tachycardia (SVT)** (to restore normal sinus rhythm) - **Diagnostic tool**: Helps differentiate between atrial and ventricular arrhythmias.
Dosing and Administration	- **Initial dose**: 6 mg IV bolus - **Second dose** (if needed): 12 mg IV bolus - **Maximum dose**: 18 mg
Onset and Duration	- **Onset**: Immediate (within 10–30 seconds) - **Duration**: Very short (10–15 seconds)
Side Effects	- **Cardiovascular**: Transient bradycardia, chest pain, hypotension - **Respiratory**: Dyspnea, bronchospasm (rare) - **CNS**: Dizziness, flushing, headache
Contraindications	- **Second- or third-degree AV block** (without a pacemaker) - **Severe asthma** or **COPD** (risk of bronchospasm) - **Sick sinus syndrome** (unless pacemaker is present)
Monitoring	- Continuous **ECG monitoring** during and after administration. - Monitor for **transient asystole** or bradycardia.
Drug Interactions	- **Theophylline**: Reduces adenosine's efficacy. - **Dipyridamole**: Increases the effects of adenosine.
Clinical Notes	- May cause **transient asystole** (normal and expected for a few seconds). - Used as a **first-line treatment** for acute SVT due to its rapid onset and short duration. - If adenosine fails, consider **calcium channel blockers** (e.g., verapamil) or **beta-blockers**.

Adenosine is a coronary vasodilator (which is why we use it in cardiac stress testing) and a bronchoconstrictor (action opposed by theophylline).

Flecainide

Attribute	Details
Class	Class Ic Antiarrhythmic (Sodium channel blocker)
Mechanism of Action	- **Inhibits sodium channels**, slowing depolarization (Phase 0) - Markedly slows conduction in atrial and ventricular tissue without affecting repolarization
Indications	- **Atrial fibrillation (AF)**: Rhythm control in structurally normal hearts - **Supraventricular tachycardia (SVT)** - **Paroxysmal AF** - **Ventricular arrhythmias** (in the absence of structural heart disease)
Dosing and Administration	- **Oral**: 50–150 mg twice daily - **Maximum dose**: 300 mg daily
Onset and Duration	- **Onset**: Within 1–2 hours (oral) - **Half-life**: 12–20 hours
Side Effects	- **Cardiovascular**: Proarrhythmia, bradycardia, hypotension - **CNS**: Dizziness, blurred vision, headache - **GI**: Nausea, metallic taste
Contraindications	- **Structural heart disease** (e.g., previous MI, heart failure) - **Severe AV block** - **Long QT syndrome**
Monitoring	- Regular **ECG** to monitor for QT prolongation or conduction block - Monitor **plasma levels** in renal or hepatic impairment
Drug Interactions	- **Beta-blockers**: Increased risk of bradycardia - **Amiodarone**: Increases flecainide plasma levels
Clinical Notes	- **Pill-in-the-pocket** approach: Used as a single dose (200–300 mg) for paroxysmal AF termination in low-risk patients. - Avoid in patients with **structural heart disease** due to proarrhythmic risk. - Typically used in combination with **beta-blockers** or **calcium channel blockers** to prevent tachycardia.

Amiodarone

Attribute	Details
Class	Class III Antiarrhythmic (Potassium channel blocker)
Mechanism of Action	- **Blocks potassium channels** → Prolongs repolarization and action potential duration - **Inhibits sodium and calcium channels and beta-receptors**, providing a broad antiarrhythmic effect
Indications	- **Atrial fibrillation** (AF) - **Ventricular arrhythmias** (VT/VF) - **Supraventricular tachycardia (SVT)** - Used in both **acute and chronic** arrhythmia management
Dosing and Administration	- **Loading dose (IV)**: 150 mg over 10 minutes, followed by 1 mg/min infusion - **Oral maintenance dose**: 200–400 mg daily
Onset and Duration	- **Onset**: Hours (IV), Days to weeks (oral) - **Half-life**: 20–100 days (very long)
Side Effects	- **Cardiovascular**: Bradycardia, QT prolongation, hypotension - **Pulmonary**: Pulmonary fibrosis - **Thyroid**: Hypothyroidism or hyperthyroidism - **Hepatic**: Elevated liver enzymes - **Ocular**: Corneal deposits, visual disturbances
Contraindications	- **Severe bradycardia** - **Prolonged QT interval** - **Thyroid dysfunction** - **Severe liver disease**
Monitoring	- **ECG** for QT interval and heart rate - **Liver function tests** (LFTs) - **Thyroid function tests** (TFTs) - **Pulmonary function tests** (for long-term therapy)
Drug Interactions	- Interacts with **warfarin, digoxin**, and **beta-blockers** (increased toxicity) - Risk of **torsades de pointes** when combined with other QT-prolonging drugs
Clinical Notes	- Requires **close monitoring** due to multiple organ toxicities. - Used cautiously in **elderly patients** and those with thyroid or liver disorders. - **IV amiodarone** preferred for acute arrhythmias; **oral** for chronic management.

Dobutamine & Dopamine

Attribute	Dobutamine	Dopamine
Class	Beta-adrenergic agonist	Dopamine receptor and adrenergic agonist
Mechanism of Action	- **Beta-1 activation**: Increases heart rate and myocardial contractility - **Minimal effect** on peripheral vasculature	- **Low dose**: Stimulates dopamine receptors → renal vasodilation - **Moderate dose**: Activates beta-1 receptors → increases heart rate and contractility - **High dose**: Activates alpha-1 receptors → vasoconstriction
Indications	- **Acute heart failure** - **Cardiogenic shock** - **Severe systolic dysfunction**	- **Shock** (cardiogenic or septic) - **Hypotension** - **Heart failure** (if associated with low cardiac output and low blood pressure)
Dosing	2.5–20 mcg/kg/min IV infusion	2–20 mcg/kg/min IV infusion (adjust based on response)
Onset and Duration	- **Onset**: 1–2 minutes - **Duration**: Minutes (stops shortly after discontinuation)	- **Onset**: Within 5 minutes - **Duration**: Less than 10 minutes after stopping
Side Effects	- Tachycardia - Arrhythmias - Hypotension (due to vasodilation)	- Tachycardia - Arrhythmias - Hypertension (at high doses) - Nausea, vomiting
Contraindications	- **Aortic stenosis** (due to increased oxygen demand) - Hypovolemia (must correct first)	- **Tachyarrhythmias** - Pheochromocytoma - Uncontrolled hypertension
Monitoring	- Continuous **ECG and blood pressure** monitoring - Monitor for **tachyarrhythmias**	- Monitor **urine output** at low doses (renal perfusion) - Continuous **ECG and blood pressure** monitoring

Adrenaline

Attribute	Details
Mechanism of Action	- **Alpha-1 receptors**: Vasoconstriction → increases blood pressure - **Beta-1 receptors**: Increases heart rate and myocardial contractility - **Beta-2 receptors**: Bronchodilation and smooth muscle relaxation
Indications	- **Cardiac arrest** - **Anaphylaxis** (if IM route ineffective) - **Severe asthma** unresponsive to standard treatments - **Severe hypotension/shock** not responding to fluids
Dosing and Administration	**Cardiac Arrest**: 1 mg every 3–5 minutes (IV bolus) **Anaphylaxis**: 0.5 mg slow IV bolus **Severe Asthma**: 0.1–0.5 mg IV infusion **Shock/Hypotension**: 0.05–2 mcg/kg/min IV infusion
Side Effects	- **Cardiovascular**: Tachycardia, arrhythmias, hypertension, myocardial ischemia - **CNS**: Anxiety, restlessness, tremors - **Local**: Tissue necrosis with extravasation - **Metabolic**: Hyperglycemia, lactic acidosis
Contraindications	- **Uncontrolled hypertension** - **Tachyarrhythmias** - **Ischemic heart disease** (use with caution) - **Narrow-angle glaucoma** (use with caution)
Monitoring and Precautions	- Monitor **ECG and blood pressure** during administration - Monitor **blood glucose** in diabetic patients - Use **central line** for continuous IV infusion to avoid extravasation - Correct **hypovolemia** before using adrenaline for shock
Clinical Notes	- **Essential in resuscitation protocols** (Advanced Life Support). - Adjust dose based on patient response.

Digoxin toxicity

Key Points

- Plasma concentration alone does **not** determine toxicity.
- Toxicity likelihood increases progressively from **1.5 to 3 mcg/l** (BNF).
- More accurate plasma samples are obtained **6 hours** after dosing.
- Mechanism of tachyarrhythmias: **Inhibition of the sodium-potassium ATPase pump.**

Clinical Features

System	Symptoms
General	Lethargy, anorexia, general unwell feeling
Gastrointestinal	Nausea, vomiting, diarrhoea (cholinergic effects)
CNS	Confusion, yellow-green vision (visual disturbances)
Cardiac	Arrhythmias: AV block, bradycardia, any abnormal rhythm (except Type II second-degree AV block)

Precipitating Factors

Factors	Details
Electrolyte disturbances	Hypokalaemia, hyperkalaemia, hypomagnesaemia, hypercalcaemia, hypernatraemia
Renal impairment	Digoxin is renally cleared; impairment increases toxicity risk
Drugs	Amiodarone, quinidine, verapamil, diltiazem, spironolactone, ciclosporin, thiazides, loop diuretics (cause hypokalaemia)
Others	Increasing age, myocardial ischaemia, acidosis, hypoalbuminaemia, hypothyroidism, amyloidosis, hypothermia

Management

1. **Monitoring**
   - Treatment guided by **clinical signs and symptoms**, not plasma concentration alone.
   - Monitor **pulse rate** to assess efficacy.
2. **Initial Treatment**
   - **Activated charcoal**: First line if ingestion occurred within **1 hour**.
   - **Binding resins** (e.g., cholestyramine): Useful for chronic toxicity with renal insufficiency.
3. **Correct Electrolyte Imbalance**
   - **Acute toxicity**: Hyperkalaemia (>5 mEq/L) → Use **digoxin-specific Fab fragments** (Digibind).
   - **Chronic toxicity**: Hypokalaemia and hypomagnesaemia → Correct both to prevent refractory hypokalaemia.
4. **Antidote ("KLAM")**
   - **K+** slowly normalised.
   - **Lidocaine**: For tachyarrhythmias if Fab therapy fails.
   - **Anti-digoxin Fab fragments**: First-line for severe toxicity (e.g., hemodynamically unstable arrhythmias, high serum digoxin levels, end organ damage).
   - **Mg2+**: Use cautiously, especially in bradycardia or renal failure.
5. **Arrhythmia Management**
   - **Severe bradycardia**: Atropine for unstable bradyarrhythmic patients.
   - **Ventricular arrhythmias**:
     - **First line**: Digoxin immune Fab.
     - **Alternative**: Lidocaine or phenytoin (Class IB agents).
     - **Avoid**: Amiodarone, calcium channel blockers, and quinidine (increase digoxin levels).
   - **Electrical cardioversion**: Avoid in VT as it may precipitate VF or asystole.
6. **When to Use Digoxin-Specific Antibodies (Digibind)**
   - **Criteria**:
     - Hemodynamically unstable arrhythmia.
     - End organ damage.
     - **Chronic ingestion**: Serum digoxin >4 ng/ml.
     - **Acute ingestion**: Serum digoxin >10 ng/ml (6 hours post-ingestion).
     - Hyperkalaemia >5 mEq/L (refractory to insulin-dextrose).
7. **Other Considerations**
   - **Dialysis**: Ineffective in removing digoxin.
   - **Adverse effect** of Fab therapy: Serum sickness.

Antiplatelets

Antiplatelets

Overview of antiplatelet agents

Overview of antiplatelet agents			
Group	**Agents**	**Indications**	**Adverse effects**
Irreversible cyclooxygenase inhibitors	Acetylsalicylic acid (aspirin)	• Acute coronary syndrome • Ischemic stroke • Primary and secondary prevention of cardiovascular disease	• Reye syndrome • Aspirin exacerbated respiratory disease • GI upset • Salicylate toxicity • Affects the kidneys in a dose-dependent manner ⇨ Low doses → uric acid retention ⇨ High doses → uric acid excretion
P2Y12 receptor antagonists (ADP receptor inhibitors)	• Clopidogrel • Prasugrel • Ticagrelor • Ticlopidine • Cangrelor	• Dual antiplatelet therapy (with acetylsalicylic acid) in ACS • Alternative to aspirin	• Allergic reactions • Haemorrhage • GI upset
Glycoprotein IIb/IIIa inhibitors	• Abciximab • Eptifibatide • Tirofiban	• High-risk patients with unstable angina/NSTEMI before undergoing PCI	• Acute thrombocytopenia • Haemorrhage

Updated Guidance on Antiplatelet Therapy (UK Guidelines)

Diagnosis	1st Line	2nd Line
NSTEMI	Aspirin (lifelong) + Clopidogrel (12 months)	Clopidogrel (lifelong) if aspirin contraindicated
STEMI	- **Aspirin (lifelong)** + Clopidogrel: - 1 month (if no or bare-metal stent) - 12 months (if drug-eluting stent)	Clopidogrel (lifelong) if aspirin contraindicated
TIA	Clopidogrel (lifelong)	Aspirin + Dipyridamole (both lifelong)
Ischaemic Stroke	Clopidogrel (lifelong)	Aspirin + Dipyridamole (both lifelong)
Peripheral Arterial Disease	Clopidogrel (lifelong)	Aspirin (lifelong)

Perioperative Management of Antiplatelet Therapy

Therapy	Perioperative Management
Aspirin	- **Low-risk bleeding surgeries**: Continue aspirin. - **High-risk surgeries**: Stop 5–7 days prior and restart 24 hours post-surgery if bleeding risk is controlled.
Clopidogrel and Other P2Y12 Inhibitors (e.g., Ticagrelor, Prasugrel)	- Stop **5–7 days** before surgery. - Restart 24 hours post-surgery if haemostasis achieved. - If high thrombotic risk, discuss with a specialist.
Dual Antiplatelet Therapy (DAPT) (Aspirin + Clopidogrel/Prasugrel/Ticagrelor)	- Elective surgery: Delay until **DAPT course completed** (e.g., 12 months for stents). - Urgent surgery: Continue aspirin and stop P2Y12 inhibitor 5 days prior if possible.

Acetylsalicylic acid (ASA, aspirin)

Attribute	Details
Mechanism of Action	- Blocks **COX-1 and COX-2**, inhibiting prostaglandin, prostacyclin, and thromboxane synthesis - Irreversibly inhibits platelet aggregation by blocking **thromboxane A2 (TXA2)** production for 7–10 days (life of platelet)
Effects by Dose	- **Low dose (<300 mg/day)**: Inhibits platelet aggregation (antithrombotic) - **Intermediate dose (300–2400 mg/day)**: Antipyretic and analgesic - **High dose (2400–4000 mg/day)**: Anti-inflammatory
Clinical Indications	- **Ischaemic heart disease** (first-line) - Secondary prevention in cardiovascular disease - Prevents stroke and TIA
Side Effects	- **Bleeding risk** (↑ bleeding time, no effect on PT/PTT) - **Hypersensitivity**: Angioedema, bronchospasm, urticaria - **Reye syndrome** (in children <19 years with viral illness) - **Gastrointestinal**: Dyspepsia, GI bleeding
Drug Interactions	Potentiates effects of **oral hypoglycemics**, **warfarin**, and **steroids**
Contraindications	- **Children** <19 years (risk of Reye syndrome, except Kawasaki disease) - **Pregnancy**: Avoid due to Reye syndrome risk in the baby (not safe for breastfeeding)

Reye syndrome

Attribute	Details
Definition	A rare **hepatic encephalopathy** associated with aspirin use in children with viral infections.
Aetiology	- Aspirin use in children <19 years with viral illnesses (e.g., influenza, varicella).
Pathophysiology	- Accumulation of salicylate metabolites → **mitochondrial injury** - Inhibition of enzymes needed for fatty acid oxidation → **acute encephalopathy** - **Hyperammonemia** → cerebral edema → increased intracranial pressure (ICP).
Features	- Preceding viral infection (e.g., influenza, varicella, viral gastroenteritis) - Acute encephalopathy - Severe vomiting, lethargy, confusion - Coma - Hepatomegaly and liver failure - Fatty degeneration of the liver
Diagnostics	- Clinical diagnosis (diagnosis of exclusion) - ↑ **AST, ALT** - **Hyperammonemia** - **Hypoglycemia** - **Liver biopsy**: Microvesicular hepatic steatosis
Treatment	- **Supportive care**: Manage airway, breathing, and circulation (ABC). - **IV fluids**: Correct hypoglycemia and electrolyte imbalances. - **Mannitol or hypertonic saline**: To reduce **intracranial pressure**. - **Vitamin K or fresh frozen plasma**: For coagulopathy management. - Monitor for **seizures** and treat as necessary.
Prevention	- **Avoid aspirin** in children <19 years (except in **Kawasaki disease**).
Prognosis	- **Mortality rate**: ~20% - Early diagnosis and supportive treatment improve outcomes.

Salicylate overdose

Attribute	Details
Key Concept	- Salicylate overdose causes **mixed respiratory alkalosis and metabolic acidosis**. - Early respiratory alkalosis due to respiratory centre stimulation. - Later, metabolic acidosis occurs due to salicylate accumulation and oxidative phosphorylation disruption.
Early Features	- **Hyperventilation** → respiratory alkalosis - **Tinnitus** (plasma salicylate >400–500 mg/L) - Sweating, fever - Vertigo, lethargy - Peripheral vasodilation, bounding pulse - Nausea, vomiting, dehydration

Attribute	Details
Later Features	- **Metabolic acidosis** - **Hypoglycemia** (more common in children) - Hyperglycemia (possible) - Seizures, coma - Pulmonary edema, acute renal failure
Diagnostics	- **Arterial blood gases (ABG)**: Mixed respiratory alkalosis and metabolic acidosis - **Salicylate plasma concentration** >700 mg/L indicates severe toxicity - Monitor electrolytes and glucose levels
Management	- **Activated charcoal**: Multiple doses if bezoars suspected to prevent delayed absorption. - **Urinary alkalinization**: IV sodium bicarbonate (1.25% or 8.4%) to enhance salicylate excretion (target urine pH 7.5–8). - **Supportive care**: Correct electrolyte imbalances and fluid loss.
Indications for Haemodialysis	- **Salicylate concentration** >700 mg/L - **Severe metabolic acidosis** resistant to treatment - Acute **renal failure** - **Pulmonary edema** - **Neurological symptoms**: Coma, seizures, hallucinations

The mixed respiratory alkalosis and metabolic acidosis in a sweaty, confused patient point towards salicylate overdose.
The development of pulmonary edema suggests severe poisoning and is an indication for hemodialysis.

Tinnitus is characteristic and salicylate toxicity may produce deafness.

Clopidogrel

Attribute	Details
Class	**Antiplatelet** agent, P2Y12 receptor inhibitor
Mechanism of Action	- Irreversibly inhibits **P2Y12 ADP receptors** on platelets, preventing platelet aggregation. - Onset of action: 2 hours after oral administration.
Indications	- **Acute Coronary Syndromes** (ACS) - **Myocardial Infarction (MI)** - **Stroke or TIA prevention** - **Peripheral arterial disease**
Dosing	- **Loading dose**: 300–600 mg (for ACS) - **Maintenance dose**: 75 mg once daily
Duration of Therapy	- **NSTEMI/STEMI**: 12 months with aspirin (DAPT) - **Ischaemic stroke/TIA**: Lifelong monotherapy

Attribute	Details
Side Effects	- **Bleeding risk** (most common) - **Gastrointestinal symptoms**: Dyspepsia, abdominal pain - **Rash** and itching
Drug Interactions	- **Proton pump inhibitors** (e.g., omeprazole) may reduce clopidogrel activation. - **Anticoagulants**: Increased bleeding risk.
Contraindications	- **Active bleeding** (e.g., GI bleeding) - **Severe liver impairment**
Monitoring	- Monitor for **signs of bleeding** - Assess **platelet function** if necessary (in cases of suspected resistance).
Clinical Notes	- Used as an alternative to aspirin in **aspirin-allergic** patients. - Part of **dual antiplatelet therapy (DAPT)** with aspirin in ACS.

Most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK

Prasugrel

Attribute	Details
Class	**Antiplatelet agent**, P2Y12 receptor inhibitor (thienopyridine class)
Mechanism of Action	- **Irreversibly inhibits P2Y12 ADP receptors** on platelets, preventing platelet aggregation. - Faster onset and more potent than clopidogrel.
Indications	- **Acute Coronary Syndromes (ACS)** managed with **percutaneous coronary intervention (PCI)** - Used in combination with aspirin as part of **dual antiplatelet therapy (DAPT)**
Dosing	- **Loading dose**: 60 mg once - **Maintenance dose**: 10 mg daily (5 mg daily for patients <60 kg)
Duration of Therapy	- **Post-PCI**: Typically for **12 months** in ACS patients
Side Effects	- **Bleeding risk** (higher than clopidogrel) - Gastrointestinal symptoms: Nausea, diarrhea - Rare: Rash, hypersensitivity
Contraindications	- **History of stroke or TIA** (due to increased bleeding risk) - **Active bleeding** - **Severe hepatic impairment**
Drug Interactions	- **Anticoagulants**: Increased risk of bleeding - Avoid with other antiplatelets unless indicated (DAPT)
Monitoring	- Monitor for **bleeding signs** and adjust therapy accordingly.
Clinical Notes	- More effective than clopidogrel but with a higher bleeding risk. - **Not recommended for elderly patients (>75 years)** or those with low body weight unless specifically indicated.

Ticagrelor

Attribute	Details
Class	**Antiplatelet agent**, reversible P2Y12 receptor inhibitor
Mechanism of Action	- **Reversibly inhibits P2Y12 ADP receptors** on platelets, preventing platelet aggregation. - Faster onset and more potent than clopidogrel.
Indications	- **Acute Coronary Syndromes (ACS)** - **Post-Myocardial Infarction (MI)** (for secondary prevention)
Dosing	- **Loading dose**: 180 mg once - **Maintenance dose**: 90 mg twice daily (for 12 months post-ACS)
Onset & Duration	- Rapid onset within 30 minutes - Reversible action with half-life of 7–12 hours
Side Effects	- **Bleeding** (higher risk than clopidogrel) - **Dyspnea** (shortness of breath) - Headache, dizziness
Contraindications	- **Active bleeding** (e.g., GI bleed) - **Severe hepatic impairment** - Co-administration with strong CYP3A4 inhibitors
Drug Interactions	- Avoid with **CYP3A4 inhibitors** (e.g., ketoconazole) - **Increases bleeding risk** when combined with anticoagulants or NSAIDs
Monitoring	- Monitor for **bleeding** and **dyspnea** - Check for drug interactions, especially with CYP3A4 modulators
Clinical Notes	- Used as an alternative to clopidogrel in **dual antiplatelet therapy (DAPT)** with aspirin. - **No need for genetic testing** like clopidogrel (not dependent on CYP2C19 activation).

Abciximab

Attribute	Details
Class	**Antiplatelet agent**, Glycoprotein IIb/IIIa receptor antagonist
Mechanism of Action	- **Binds to glycoprotein IIb/IIIa receptors** on platelets, preventing fibrinogen and von Willebrand factor from binding. - Inhibits platelet aggregation by blocking the final common pathway of platelet activation.
Indications	- **Adjunctive therapy in PCI** (percutaneous coronary intervention) - **Unstable angina** refractory to conventional therapy - **Acute coronary syndromes (ACS)**
Dosing	- **IV bolus**: 0.25 mg/kg - Followed by **continuous infusion**: 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 hours
Onset & Duration	- Immediate onset after IV administration - Platelet function returns to normal within **24–48 hours** after discontinuation
Side Effects	- **Bleeding** (major complication) - Thrombocytopenia - Hypersensitivity reactions

Attribute	Details
Contraindications	- **Active bleeding** (e.g., recent GI bleed) - **History of stroke within 30 days** or hemorrhagic stroke - Severe **uncontrolled hypertension** - Recent major surgery or trauma
Monitoring	- Monitor **platelet count** for thrombocytopenia - Assess for **signs of bleeding** throughout therapy
Drug Interactions	- Increased bleeding risk with **anticoagulants** and **other antiplatelet agents**
Clinical Notes	- Primarily used during **PCI** to reduce the risk of thrombotic complications. - Not typically used for long-term antiplatelet therapy.

Anti-hypertensive drugs

Angiotensin-converting enzyme (ACE) inhibitors

Attribute	Details
Mechanism of Action	- Inhibit **angiotensin-converting enzyme (ACE)**, blocking the conversion of **angiotensin I to angiotensin II** - Reduces vasoconstriction, aldosterone release, and sodium retention - Increases bradykinin levels, promoting vasodilation but causing cough and angioedema
Indications	- **Hypertension:** First-line therapy, especially in patients with diabetes or CKD - **Heart Failure (HFrEF)**: Improves symptoms, reduces mortality and hospitalizations - **Post-MI**: Prevents ventricular remodelling and recurrent MI - **Chronic Kidney Disease (CKD)**: Slows progression and reduces proteinuria - **Diabetic Nephropathy**: Reduces albuminuria
Side Effects	- Persistent **dry cough** (due to bradykinin accumulation) - **Angioedema** (rare but serious) - **Hyperkalemia** - Hypotension, dizziness - Acute kidney injury (AKI) in high-risk patients
Contraindications	- **Pregnancy** (teratogenic) - **Bilateral renal artery stenosis** (risk of renal failure) - History of **angioedema** with ACE inhibitors

Attribute	Details
Advantages	- **Cardioprotective:** Reduces mortality in heart failure and post-MI patients - **Renal protection**: Reduces proteinuria and delays CKD progression - Effective in both **hypertensive** and **diabetic** patients
Common ACE Inhibitors	- **Ramipril**: Cardiovascular protection, once-daily dosing - **Enalapril**: Common in heart failure - **Lisinopril**: Long half-life, suitable for hypertension - **Perindopril**: Cardiovascular risk reduction
Comparison with ARBs	- ACE inhibitors are **first-line** due to more clinical evidence - ARBs are preferred if patients experience **cough** or **angioedema** with ACE inhibitors - Both ACE inhibitors and ARBs provide **similar renal and cardiovascular benefits**

Comparison of ACE Inhibitors: Summary Table

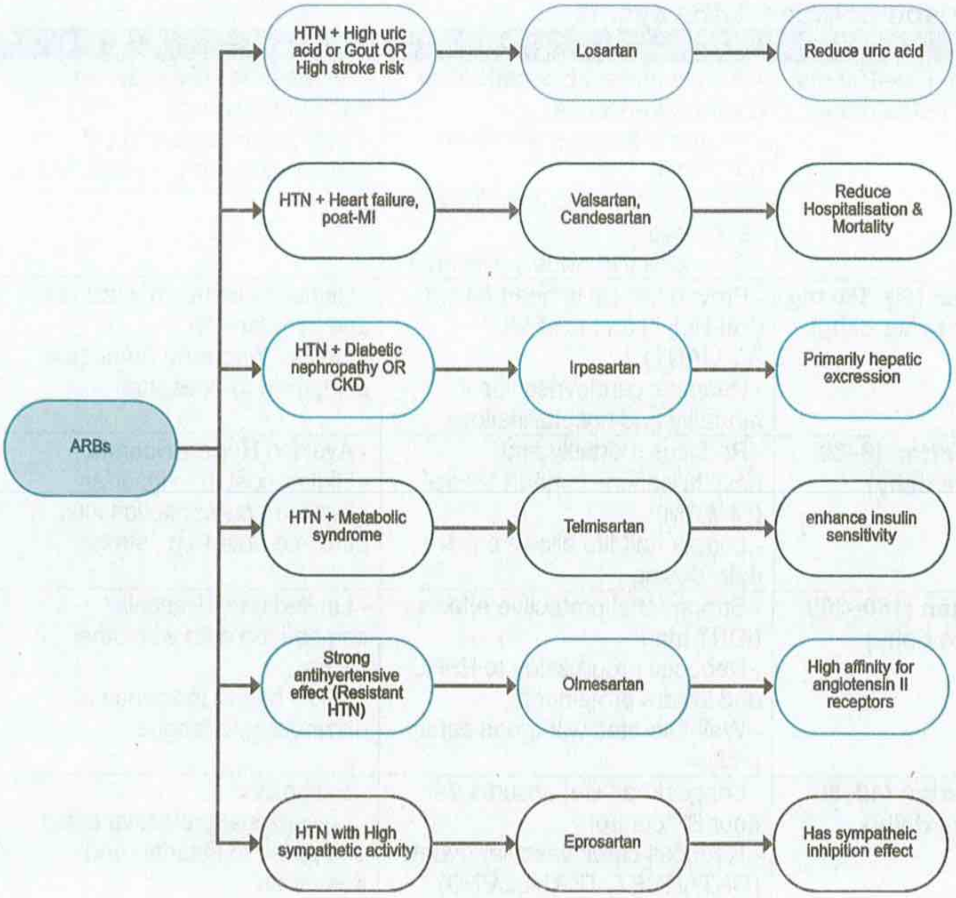
ACE Inhibitor (Dose)	Advantages	Disadvantages
Ramipril (2.5–10 mg once daily)	- Strong cardiovascular protection - Reduces mortality in heart failure and post-MI - Once-daily dosing	- Can cause cough and angioedema - Requires dose adjustment in renal impairment
Enalapril (5–20 mg twice daily)	- Proven benefit in heart failure - Reduces mortality and hospitalizations (CONSENSUS and SOLVD trials)	- Twice-daily dosing needed - May cause hypotension and hyperkalemia
Lisinopril (10–40 mg once daily)	- Long half-life, suitable for hypertension - Effective in reducing blood pressure and proteinuria	- Higher risk of hyperkalemia - May take longer to reach therapeutic effect compared to other ACE inhibitors
Perindopril (4–8 mg once daily)	- Proven benefit in cardiovascular risk reduction (EUROPA trial) - Long half-life allows once-daily dosing	- More expensive than older ACE inhibitors - Cough and angioedema still possible
Captopril (25–100 mg 2-3 times daily)	- Rapid onset of action, useful in hypertensive emergencies - Short half-life allows easier titration	- Requires frequent dosing (2-3 times daily) - More prone to side effects (cough, rash, taste disturbance)

Angiotensin-II Receptor Blockers (ARBs)

Attribute	Details
Mechanism of Action	- Block **AT1 receptor**, reducing vasoconstriction and aldosterone release - Activate **AT2 receptors**, promoting vasodilation - Do not interfere with **bradykinin metabolism** (less dry cough, angioedema)
Indications	- **Hypertension** (first-line for ACEi-intolerant patients) - **Heart Failure (HFrEF)** - **Chronic Kidney Disease** with proteinuria - **Post-MI** - **Diabetic Nephropathy**
Side Effects	- Dizziness, fatigue, hypotension - Hyperkalemia (especially in CKD) - Rare: Angioedema (though less likely than with ACE inhibitors)
Contraindications	- Pregnancy (teratogenic) - Bilateral renal artery stenosis (risk of renal failure) - Severe hyperkalemia
Advantages	- **Renal protection**: Reduces proteinuria and slows CKD progression - **Cardiovascular benefits**: Lowers stroke, MI, and heart failure risk - **Better tolerated**: No bradykinin accumulation, fewer cases of cough or angioedema
Common ARBs	- **Losartan**: Stroke prevention - **Valsartan**: Heart failure, post-MI - **Candesartan**: Cardiovascular risk reduction - **Irbesartan, Telmisartan**: Renal benefits in diabetic nephropathy
Comparison with ACE Inhibitors	- ARBs preferred if ACE inhibitors cause **cough** or **angioedema** - ACE inhibitors remain **first-line** due to more clinical evidence - ARBs offer similar efficacy with **better tolerance**

Comparison between ARBs agents

ARB	Advantages	Disadvantages
Losartan (50–100 mg once or twice daily)	- Lowers uric acid; beneficial for gout/hyperuricemia - Proven in stroke prevention (LIFE trial) - Reduces proteinuria in diabetic nephropathy - Cost-effective, widely available	- Shortest half-life; may require twice-daily dosing - Slightly less potent in BP control compared to other ARBs
Valsartan (80–160 mg once or twice daily)	- Proven benefit in heart failure (Val-HeFT) and post-MI (VALIANT) - Reduces cardiovascular mortality and hospitalisations	- Higher incidence of dizziness and hypotension - Limited long-term renal data compared to irbesartan
Candesartan (8–32 mg once daily)	- Reduces mortality and hospitalisations in heart failure (CHARM) - Longer half-life allows once-daily dosing	- Avoid in **Hyperuricemia** - Higher cost than losartan - Limited non-cardiovascular outcome data (e.g., stroke)
Irbesartan (150–300 mg once daily)	- Strong renal protective effects (IDNT trial) - Reduces progression to ESRD and lowers proteinuria - Well-tolerated with good safety profile	- Limited cardiovascular comparison data with other ARBs - Mildly higher incidence of dizziness and fatigue
Telmisartan (40–80 mg once daily)	- Longest half-life; ensures 24-hour BP control - Reduces cardiovascular events (ONTARGET, TRANSCEND) - Potential lipid-modulating effects	- Expensive - Lower renal protective effect compared to losartan and irbesartan
Olmesartan (20–40 mg once daily)	- Most potent BP-lowering ARB - Good 24-hour efficacy with once-daily dosing	- Avoid in **Diabetic nephropathy** - Associated with sprue-like enteropathy (chronic diarrhoea, weight loss) - Limited long-term cardiovascular outcome data - should be avoided in


ARBs
HTN + High uric acid or Gout OR High stroke risk
Losartan
Reduce uric acid
HTN + Heart failure, poat-MI
Valsartan, Candesartan
Reduce Hospitalisation & Mortality
HTN + Diabetic nephropathy OR CKD
Irpesartan
Primarily hepatic excression
HTN + Metabolic syndrome
Telmisartan
enhance insulin sensitivity
Strong antihyertensive effect (Resistant HTN)
Olmesartan
High affinity for angiotensin II receptors
HTN with High sympathetic activity
Eprosartan
Has sympatheic inhipition effect

Beta-blockers

Attribute	Details
Classes	- **Non-selective**: Propranolol, Carvedilol, Labetalol - **Cardio-selective (β1-selective)**: Atenolol, Bisoprolol, Metoprolol - **With additional effects**: Carvedilol (α-blocking), Nebivolol (NO-mediated vasodilation)
Mechanism of Action	Block **β-adrenergic receptors**, reducing heart rate and myocardial contractility, and inhibiting renin release from the kidneys.
Indications	- **Hypertension** - **Heart failure** (Bisoprolol, Carvedilol, Metoprolol) - **Angina** - **Arrhythmias** (e.g., atrial fibrillation) - **Post-myocardial infarction** (reduces mortality) - **Migraine prophylaxis** (Propranolol)
Pharmacokinetics	- **Atenolol**: Hydrophilic, renally excreted - **Propranolol**: Lipophilic, crosses the blood-brain barrier - **Bisoprolol**: Once-daily dosing due to long half-life
Side Effects	- Bradycardia, fatigue, dizziness - Cold extremities, Raynaud's phenomenon - Bronchospasm (in non-selective beta-blockers) - Sexual dysfunction, insomnia, depression (especially lipophilic beta-blockers like propranolol)
Contraindications	- Severe bradycardia - Heart block >1st degree (without pacemaker) - Asthma (non-selective beta-blockers) - Cardiogenic shock
Drug Interactions	- **Non-dihydropyridine CCBs** (e.g., Verapamil, Diltiazem): Risk of severe bradycardia or heart block - **Insulin and oral hypoglycemics**: May mask symptoms of hypoglycaemia (e.g., tachycardia)
Monitoring	- **Heart rate** and **blood pressure** regularly - Monitor for signs of **bronchospasm** in asthmatics
Withdrawal Considerations	**Gradual tapering** is required to avoid rebound hypertension, tachycardia, or angina.
Other Notes	- **Carvedilol** and **Bisoprolol** are preferred in heart failure with reduced ejection fraction. - **Nebivolol** offers additional vasodilatory benefits, useful in hypertensive patients with endothelial dysfunction.

Calcium channel blockers

Attribute	Details
Classes	- **Dihydropyridines**: Amlodipine, Nifedipine, Felodipine - **Non-dihydropyridines**: Verapamil, Diltiazem
Mechanism of Action	Block L-type calcium channels in vascular smooth muscle and myocardium, leading to **vasodilation** and decreased myocardial contractility.
Indications	- **Hypertension** - **Angina** (both stable and Prinzmetal's angina) - **Arrhythmias** (non-dihydropyridines: atrial fibrillation, atrial flutter) - Raynaud's phenomenon (dihydropyridines)
Pharmacokinetics	- **Amlodipine**: Long half-life, once-daily dosing - **Verapamil/Diltiazem**: Extensively metabolized in the liver
Side Effects	- **Dihydropyridines**: Flushing, headache, ankle oedema, reflex tachycardia - **Non-dihydropyridines**: Bradycardia, heart block, constipation (especially Verapamil)
Contraindications	- **Dihydropyridines**: Avoid in severe aortic stenosis (risk of worsening hypotension) - **Non-dihydropyridines**: Avoid in heart block or severe bradycardia
Drug Interactions	- **Non-dihydropyridines**: Interact with β-blockers, increasing risk of bradycardia and heart block - Both classes can interact with **grapefruit juice** (increases drug levels)
Monitoring	- **Blood pressure** regularly - **Heart rate** for non-dihydropyridines to monitor bradycardia
Withdrawal Considerations	Sudden withdrawal may cause **rebound hypertension**. Gradual tapering is recommended.
Other Notes	- Dihydropyridines are more **vasoselective** (preferred for hypertension). - Non-dihydropyridines are more **cardioselective** (used for arrhythmias and angina).

Alpha-adrenoceptor blockers

Attribute	Details
Mechanism of Action	Block **alpha-1 adrenergic receptors** on vascular smooth muscle, causing **vasodilation** and lowering blood pressure.
Indications	- **Hypertension**: Adjunct treatment in resistant hypertension - **Benign Prostatic Hyperplasia (BPH)**: Relieves urinary symptoms by relaxing smooth muscle in the bladder neck and prostate.
Common Alpha-Blockers	- **Prazosin**: Short-acting, used in hypertension (1–20 mg daily, in divided doses) - **Doxazosin**: Long-acting, once-daily dosing (1–16 mg once daily) - **Terazosin**: Also used for BPH and hypertension (1–20 mg once daily) - **Tamsulosin:** Highly selective for alpha-1A receptors in the prostate and bladder neck, Not effective for blood pressure control (0.4 mg once daily)

Attribute	Details
Side Effects	- **Postural hypotension**: Especially after the first dose - **Dizziness**, fatigue, headache - **Reflex tachycardia** (compensatory) - **Nasal congestion**
Contraindications	- Severe hypotension - History of **syncope** or orthostatic hypotension - Use with caution in **heart failure** (can worsen symptoms)
Advantages	- **Improves urinary symptoms** in BPH - Useful as an **add-on therapy** for resistant hypertension - Provides smooth muscle relaxation in both the vascular and urinary systems.
Disadvantages	- **First-dose hypotension**: Requires monitoring - Not recommended as **first-line treatment** for hypertension due to less evidence of reducing cardiovascular events.
Monitoring	- Monitor for **postural hypotension**, especially after the first dose. - Check **blood pressure** regularly to assess efficacy.

Direct Vasodilators (Hydralazine, Minoxidil)

Attribute	Details
Examples	Hydralazine, Minoxidil
Mechanism of Action	Relax vascular smooth muscle, primarily in arterioles → **Reduce peripheral resistance** and blood pressure
Indications	- **Resistant Hypertension** - **Heart Failure** (Hydralazine combined with nitrates)
Doses	- **Hydralazine**: 25–100 mg 2-4 times daily - **Minoxidil**: 5–40 mg daily
Side Effects	- **Hydralazine**: Reflex tachycardia, lupus-like syndrome, headache - **Minoxidil**: Reflex tachycardia, hypertrichosis (excess hair growth), fluid retention, pericardial effusion
Contraindications	- **Severe heart failure** without β-blocker and diuretic support - **Coronary artery disease** (risk of angina)
Monitoring	- Monitor **blood pressure** regularly - Check for **fluid retention** and **heart rate** (to prevent tachycardia)
Clinical Use	- **Combination therapy**: Often used with **β-blockers** to prevent tachycardia and **diuretics** to manage fluid retention - Hydralazine is preferred for **heart failure** in patients intolerant to ACEi/ARBs.

Centrally acting antihypertensives

Attribute	Details
Examples	- **Clonidine** - **Methyldopa** - **Moxonidine** - **Guanfacine**
Mechanism of Action	Stimulate **α2-adrenergic receptors** in the brainstem, reducing sympathetic outflow → Decreases peripheral resistance and heart rate, lowering blood pressure.
Indications	- Hypertension (especially resistant hypertension) - Methyldopa: Used in pregnancy-induced hypertension
Pharmacokinetics	- **Clonidine**: Oral, transdermal forms available, short half-life (administer multiple times daily) - **Methyldopa**: Prodrug, metabolised in the liver to active form - **Moxonidine**: Longer half-life than clonidine
Side Effects	- **CNS**: Sedation, dizziness, fatigue - **Cardiovascular**: Bradycardia, orthostatic hypotension - **Gastrointestinal**: Dry mouth, constipation - **Methyldopa**: Haemolytic anaemia, hepatotoxicity
Drug Interactions	- **β-blockers**: Risk of severe bradycardia if combined with clonidine - **CNS depressants**: Increased sedation - **MAO inhibitors**: Contraindicated with methyldopa (risk of hypertensive crisis)
Contraindications	- Severe bradycardia - Depression (clonidine) - Liver disease (methyldopa)
Monitoring	- **Blood pressure** and **pulse rate** regularly - Monitor liver function with methyldopa
Withdrawal Considerations	Abrupt discontinuation of clonidine can cause **rebound hypertension**. Gradual tapering is recommended.
Other Notes	- Methyldopa is **safe during pregnancy** and often used for gestational hypertension - Moxonidine is preferred in patients with metabolic syndrome (less sedation and fewer CNS side effects).

Digoxin

Attribute	Details
Class	Cardiac glycoside
Mechanism of Action	Inhibits sodium-potassium ATPase pump → Increases intracellular calcium → Enhances myocardial contractility and slows AV node conduction
Indications	- Heart failure (with reduced ejection fraction) - Atrial fibrillation (rate control) - Atrial flutter (adjunct therapy)
Pharmacokinetics	- **Absorption**: 60-80% oral bioavailability - **Metabolism**: Minimal hepatic metabolism - **Elimination**: Renally excreted - **Half-life**: 36-48 hours
Therapeutic Range	0.5 - 2 ng/ml (levels above 2 ng/ml increase risk of toxicity)
Side Effects	- Gastrointestinal: Nausea, vomiting, diarrhoea - CNS: Confusion, dizziness, yellow-green vision - Cardiac: Bradycardia, AV block, arrhythmias
Drug Interactions	- **Increase levels**: Amiodarone, verapamil, quinidine, spironolactone, ciclosporin - **Hypokalaemia-inducing drugs**: Thiazides, loop diuretics (increase toxicity risk)
Monitoring Parameters	- **Pulse rate**: Regular monitoring - **Electrolytes**: Potassium, magnesium, calcium - **Renal function**: Serum creatinine
Signs of Toxicity	- Nausea, vomiting, anorexia - Yellow-green vision - Bradycardia, AV block, arrhythmias (except Type II second-degree AV block)
Management of Toxicity	- **Mild toxicity**: Dose adjustment, correct electrolytes (e.g., hypokalaemia) - **Severe toxicity**: Digoxin-specific Fab fragments (Digibind) - **Arrhythmias**: Lidocaine or phenytoin (avoid amiodarone and calcium channel blockers)
Contraindications	Ventricular fibrillation
Other Notes	- Dose adjustment required in **renal impairment** - **Activated charcoal** for overdose within 1 hour

Diuretics

Class	Compound	Action	Side effects
Loop Diuretics	Furosemide Bumetanide ethacrynic acid	inhibit **NKCC2** in the thick ascending loop of Henle	Deafness
Thiazides	hydrochlorothiazide, indapamide	inhibit **NaCl** co-transporter in early distal tubule	hyponatraemia, hypokalaemia, hypercalcaemia
K+ sparing agents	spironolactone	Aldosterone receptor antagonist	Hyperkalemia
	amiloride, **triamterene**	inhibit **Na** channel in late distal tubule	Hyperkalemia
Osmotic Diuretics	mannitol	Inhibit water reabsorption throughout the tubules, but mostly in the proximal tubule	Pulmonary edema

Loop Diuretics

Attribute	Furosemide
Agents and doses	**Furosemide** **Bumetanide** **Torasemide** **Ethacrynic Acid**
Action	Inhibits $Na^+/K^+/2Cl^-$ symporter in the ascending limb of the loop of Henle, increasing sodium, potassium, and water excretion
Side Effects	Hypokalaemia, hypovolaemia, ototoxicity, hyperuricaemia
Contraindications	Severe electrolyte depletion, anuria, sulfa allergy
Special Notes	**Ethacrynic Acid is safe in sulfa allergy**

Thiazide diuretics

Attribute	Hydrochlorothiazide	Chlorthalidone	Indapamide
Action	Inhibits sodium-chloride symporter in the distal convoluted tubule, reducing sodium reabsorption	Inhibits sodium-chloride symporter in the distal convoluted tubule, prolonging diuretic action	Inhibits sodium-chloride symporter, also has vasodilatory effects independent of diuresis
Dose	12.5-50 mg daily	12.5-25 mg daily	1.25-2.5 mg daily
Side Effects	Hypokalaemia, hyponatraemia, hypercalcaemia, hyperuricaemia, hyperglycaemia	Hypokalaemia, hyponatraemia, dizziness, hyperglycaemia	Hypokalaemia, hyponatraemia, hyperglycaemia, dizziness

Attribute	Hydrochlorothiazide	Chlorthalidone	Indapamide
Contraindications	Severe renal impairment, sulfa allergy	Severe renal impairment, sulfa allergy	Severe liver or renal disease, sulfa allergy
Other Notes	Useful in hypertension and mild edema; may increase serum uric acid	Preferred in hypertension due to prolonged action and reduced cardiovascular events	Used in hypertension and heart failure; less impact on lipid metabolism compared to others

Potassium-sparing diuretics (Amiloride and Triamterene)

Attribute	Amiloride	Triamterene
Action	Inhibits epithelial sodium channels (ENaC) in the distal nephron, preventing sodium reabsorption and potassium excretion	Blocks ENaC in the collecting ducts, reducing sodium reabsorption and preserving potassium
Dose	5-10 mg daily	50-100 mg daily
Side Effects	Hyperkalaemia, nausea, dizziness	Hyperkalaemia, kidney stones, dizziness
Contraindications	Severe renal impairment, hyperkalaemia	Renal impairment, hyperkalaemia
Other Notes	Often used in combination with thiazide or loop diuretics to prevent potassium loss	May cause nephrolithiasis (kidney stones); not preferred in chronic kidney disease

Aldosterone antagonists

Category	Details
Agents	- Spironolactone: 12.5-25 mg/day - Eplerenone: 50 mg twice daily - Finerenone: 10-40 mg/day
Action	Block the action of aldosterone, leading to increased excretion of sodium and water, and reduced potassium loss.
Indications	- Heart failure - High blood pressure - Hyperaldosteronism - Chronic kidney disease
Side Effects	- Hyperkalemia - Spironolactone has a higher risk of gynecomastia and liver toxicity - Eplerenone is similar to spironolactone but with a lower risk of gynecomastia - Finerenone has a lower risk of hyperkalemia
Contraindications	- Hyperkalemia - Addison's disease
Interactions	- Other potassium-sparing diuretics - ACE inhibitors - ARBs (Angiotensin II Receptor Blockers)

Inflammatory conditions

Acute pericarditis

Definition

- Acute pericarditis refers to inflammation of the pericardial sac, which may present with or without pericardial effusion and can occur as an isolated condition or alongside myocarditis (myopericarditis).

Clinical Features

Feature	Details
Chest Pain	Sharp, pleuritic; worse with inspiration and lying flat, relieved by leaning forward
Shoulder Pain	Referred pain via the phrenic nerve, may radiate to the trapezius
Pericardial Rub	Pathognomonic; present in 50% of cases
Associated Symptoms	Dry cough, dyspnea, flu-like symptoms

Types and Causes of Pericarditis

Type	Cause	Notes
Fibrinous Pericarditis	Viral infection (most common), MI, Dressler syndrome	Coxsackie B virus is common. Aspirin preferred post-MI.
Uremic Pericarditis	Blood urea nitrogen >60 mg/dL	No typical ECG changes. Requires urgent dialysis.
Purulent Pericarditis	Bacterial infection (Staphylococcus, Gram-negative species)	High risk of constrictive pericarditis
Hemorrhagic Pericarditis	TB, malignancy, or trauma	Associated with tamponade
Caseous Pericarditis	Tuberculosis	Frequently leads to constrictive pericarditis

Investigations

Investigation	Finding
ECG	Diffuse ST elevation, PR depression, T-wave inversion
Echocardiogram	Rule out tamponade and pericardial constriction
Blood Tests	↑ ESR, CRP, leukocytosis, troponin I

Diagnosis (ESC Guidelines): Diagnosis requires **2 out of 4** criteria:

1. Pericarditic chest pain
2. Pericardial rub
3. New widespread ST elevation or PR depression
4. Pericardial effusion

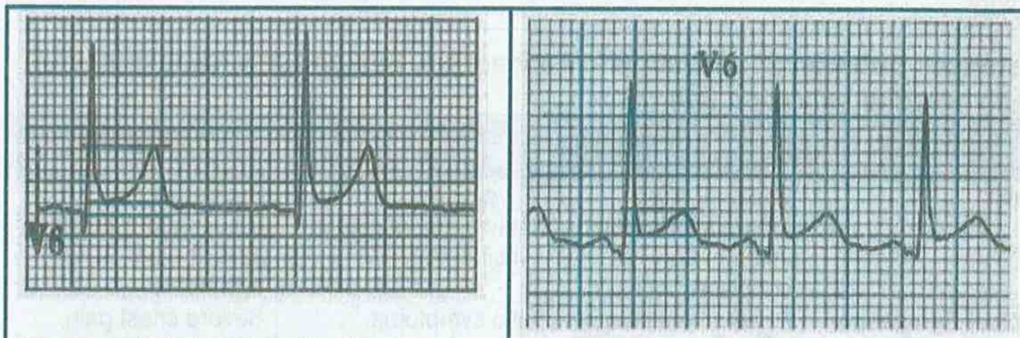
Management

Treatment Approach	Details
NSAIDs + Colchicine	NSAIDs are first-line (e.g., aspirin). Colchicine reduces recurrence rates. Continue colchicine for 3 months.
Corticosteroids	For refractory or immune-mediated pericarditis (e.g., connective tissue disease). Avoid early use.
Pericardectomy	Indicated for recurrent pericarditis unresponsive to medical therapy.
Reduce Physical Activity	Physical activity reduction recommended during treatment.

Differences Between ST Elevation in Pericarditis, Benign Early Repolarisation, and Myocardial Infarction (MI)

Feature	Pericarditis	Benign Early Repolarisation	Myocardial Infarction (MI)
Onset	Gradual, often following infection or inflammatory condition	Typically asymptomatic, found incidentally	Sudden onset, associated with chest pain or other ACS symptoms
Clinical Symptoms	Sharp chest pain relieved by sitting up or leaning forward, may have fever	No symptoms	Severe chest pain, radiates to arm, neck, or jaw, nausea, sweating
Distribution of ST Elevation	Diffuse (widespread) across many leads	Mostly in precordial leads (V2-V6)	Localised to coronary territory (e.g., inferior leads: II, III, aVF for RCA)
ST Segment Morphology	Concave upward ("saddle-shaped")	Concave upward, often prominent	Convex (tombstone shape), or horizontal
PR Segment Changes	PR segment depression, especially in inferior leads	Absent	No PR depression; may show reciprocal ST depression in opposing leads
T Wave Changes	T-wave inversion occurs after ST elevation normalizes	No T-wave inversion	T-wave inversion typically occurs after hours to days post-ST elevation
Reciprocal Changes	None or minimal	Absent	Present (ST depression in opposite leads)

Feature	Pericarditis	Benign Early Repolarisation	Myocardial Infarction (MI)
Response to Exercise	No change with exercise	ST elevation may persist but not change with exertion	Worsens with exertion; pain often increases with physical activity
Resolution	Gradual over days to weeks	Persistent over years	ST changes resolve with reperfusion or over time
Markers of Myocardial Injury (Troponin)	Mild elevation or normal	Normal	Significantly elevated
Echocardiogram Findings	May show pericardial effusion	Normal	Regional wall motion abnormalities



Benign Early Repolarisation | **Pericarditis**

Pericardial effusion

Category	Details
Definition	Abnormal accumulation of fluid in the pericardial sac surrounding the heart.
Causes	**Infectious**: Viral (Coxsackievirus), bacterial (TB, pneumonia), fungal **Autoimmune**: Rheumatoid arthritis, SLE, scleroderma **Trauma**: Post-cardiac surgery or injury **Malignancy**: Primary or metastatic cancer **Metabolic**: Hypothyroidism, uraemia **Medications**: Hydralazine, isoniazid
Pathophysiology	Excess fluid builds up within the pericardium, impairing diastolic filling and potentially causing cardiac tamponade if rapid or severe.
Clinical Features	**Small effusion**: Often asymptomatic **Larger/rapid effusion**: Chest pain, dyspnoea, orthopnoea, palpitations **Severe cases (tamponade)**: Hypotension, tachycardia, jugular venous distention (JVD), pulsus paradoxus

Category	Details
Diagnostic Approach	**ECG**: Low voltage QRS, electrical alternans (alternating QRS amplitudes) **Chest X-ray**: Enlarged cardiac silhouette ("water-bottle heart") **Echocardiogram**: Most sensitive test, showing pericardial fluid **CT/MRI**: Helpful if echocardiography is inconclusive **Pericardiocentesis**: Diagnostic fluid analysis to identify infections, malignancy, or autoimmune conditions
Complications	**Cardiac tamponade**: Life-threatening condition with impaired cardiac output Constriction of heart function due to chronic fluid accumulation
Management	**Observation**: If small and asymptomatic **Medical management**: NSAIDs, colchicine, corticosteroids (if secondary to inflammation or autoimmune disease) **Pericardiocentesis**: For symptomatic relief or tamponade **Surgical drainage**: Pericardial window for recurrent effusions or persistent symptoms

Cardiac tamponade

Aspect	Details
Definition	Accumulation of pericardial fluid under pressure, leading to impaired cardiac filling.
Beck's Triad	1. Hypotension 2. Raised JVP (absent Y descent) 3. Muffled heart sounds
Key Features	- Dyspnoea - Raised JVP (absent Y descent) - Tachycardia - Hypotension - Impalpable apex beat - Muffled heart sounds - Pulsus paradoxus - Kussmaul's sign (rare)
Investigations	- ECG: Tachycardia, low QRS voltage, electrical alternans - Chest X-ray: Enlarged cardiac silhouette - Echocardiogram: Chamber collapse, abnormal venous flows
Treatment	Pericardiocentesis
Distinguishing Feature	Hypotension is a key feature that differentiates cardiac tamponade from constrictive pericarditis.

Hypotension is the best clinical features that distinguishes cardiac tamponade from constrictive pericarditis (hypotension is a late feature in constrictive pericarditis).

Constrictive Pericarditis

Category	Details
Definition & Pathophysiology	Chronic inflammation of the pericardium leading to fibrosis and constriction of the heart, impairing diastolic filling and causing right-sided heart failure.
Risk Factors	- Previous cardiac surgery - Previous pericarditis - Radiotherapy - Connective tissue diseases
Causes	- **Tuberculous pericarditis**: Commonest cause worldwide - Mediastinal irradiation - Purulent pericarditis
Clinical Features	- **Dyspnoea** - **Right-sided heart failure**: Elevated JVP, ascites, oedema, hepatomegaly - **JVP**: Prominent x and y descent - **Pericardial knock** (loud S3) - **Kussmaul's sign**: Rise in JVP on inspiration
Investigations	- **Chest X-ray (CXR)**: Pericardial calcification; detects effusions if >250 mL - **Echocardiography**: First-line test to assess effusion and cardiac function - **Cardiac MRI/CT**: For detailed imaging if echocardiography is inconclusive - **Gold standard**: Cardiac catheterization to assess intracardiac pressures
Differentiation	**Constrictive Pericarditis vs. Cardiac Tamponade** - **JVP:** Present x and y descent in constrictive pericarditis (absent y descent in tamponade) - **Pulsus paradoxus:** Absent in constrictive pericarditis (present in tamponade) - **Kussmaul's sign:** Present in constrictive pericarditis (rare in tamponade) - **Pericardial calcification (CXR):** Seen in constrictive pericarditis
Differential Diagnosis	**Constrictive Pericarditis vs. Restrictive Cardiomyopathy** - **History**: Pericarditis vs. systemic disease (amyloidosis, hemochromatosis) - **Heart sounds**: Pericardial knock vs. loud S3 - **Apical pulse**: Non-palpable apex in constrictive pericarditis vs. prominent apical pulse in restrictive cardiomyopathy - **CXR**: Pericardial calcification in constrictive pericarditis; normal in restrictive cardiomyopathy
Treatment	**Pericardiotomy**: Surgical removal of the thickened pericardium for symptomatic relief

Constrictive Pericarditis vs. Cardiac Tamponade:

Feature	Constrictive Pericarditis	Cardiac Tamponade
Definition	Chronic fibrosis and thickening of the pericardium, limiting diastolic filling of the heart.	Accumulation of fluid in the pericardial sac, compressing the heart and limiting its function.
Causes	Tuberculosis, radiation therapy, post-cardiac surgery, viral pericarditis, idiopathic causes.	Trauma, malignancy, uremia, pericarditis, aortic dissection, or infection.
Pathophysiology	Thickened pericardium restricts the heart's ability to fill during diastole.	Fluid accumulation leads to increased intrapericardial pressure, impairing heart chambers' filling.
Onset	Chronic, gradual over time.	Acute or subacute onset (can be rapid with trauma).
Key Symptoms	Fatigue, dyspnoea, peripheral oedema, ascites, weight loss.	Tachycardia, hypotension, dyspnoea, chest pain, syncope.
Pulsus Paradoxus	Rare or absent.	Common (≥10 mmHg drop in systolic BP during inspiration).
Jugular Venous Pulse	Prominent X and Y descents (due to impaired ventricular filling).	Absent Y descent (due to impaired right atrial filling).
Kussmaul's Sign	Present (rise in JVP with inspiration).	Absent.
Heart Sounds	Pericardial knock heard in early diastole.	Distant or muffled heart sounds.
Chest X-ray/Imaging	Calcified pericardium (in some cases).	Enlarged cardiac silhouette (water-bottle appearance).
Echocardiography	Thickened pericardium, restricted ventricular filling with normal chamber sizes.	Pericardial effusion, right atrial or ventricular collapse.
Cardiac Catheterisation	Equalisation of diastolic pressures in all four chambers.	Elevated intrapericardial pressure and ventricular collapse.
Treatment	Pericardiectomy (surgical removal of the pericardium).	Emergency pericardiocentesis or surgical drainage.
Prognosis	Good with timely pericardiectomy, but may depend on underlying cause.	Potentially fatal without immediate intervention.

Comparison between Constrictive Pericarditis and Restrictive Cardiomyopathy:

Feature	Constrictive Pericarditis	Restrictive Cardiomyopathy
Definition	Chronic fibrosis and thickening of the pericardium, limiting diastolic filling of the heart.	A myocardial disorder where the ventricles become stiff, impairing diastolic filling without significant pericardial involvement.
Pathophysiology	Thickened pericardium restricts the heart's ability to fill during diastole.	Reduced myocardial compliance due to fibrosis or infiltration.

Feature	Constrictive Pericarditis	Restrictive Cardiomyopathy
Causes	Tuberculosis, radiation therapy, post-cardiac surgery, viral pericarditis, idiopathic causes.	Amyloidosis, sarcoidosis, scleroderma, endomyocardial fibrosis, hemochromatosis.
Clinical Presentation	Right heart failure symptoms: ascites, peripheral oedema, hepatomegaly, fatigue.	Symptoms of both right and left heart failure: dyspnoea, fatigue, peripheral oedema.
Key Physical Findings	**Kussmaul's sign** (rise in JVP on inspiration), **pericardial knock** (early diastolic sound).	May show **Kussmaul's sign**, but no pericardial knock.
Pulsus Paradoxus	Rare or mild.	Absent.
ECG Findings	Low voltage QRS, non-specific ST-T changes.	Low voltage QRS, possibly conduction abnormalities or arrhythmias.
Echocardiography Findings	Thickened pericardium, ventricular interdependence, and exaggerated septal shift with respiration.	Normal or thickened ventricles, biatrial enlargement, restrictive diastolic pattern.
CT / MRI Findings	Pericardial thickening (>4 mm) and calcification.	Normal pericardium, myocardial fibrosis or infiltration.
Right Heart Catheterisation	Equalisation of diastolic pressures across all four chambers.	Elevated ventricular filling pressures, restrictive filling pattern.
Treatment	Pericardiectomy (surgical removal of pericardium).	Symptom management with diuretics, treatment of underlying cause (e.g., amyloidosis).
Prognosis	Good with successful pericardiectomy.	Poor in conditions like amyloidosis; prognosis depends on the underlying cause.

Rheumatic fever

Definition:

- Rheumatic fever (RF) is an autoimmune, inflammatory disease that develops as a delayed complication of untreated or poorly treated group A beta-haemolytic streptococcal pharyngitis. It affects multiple systems, particularly the heart, joints, skin, and nervous system.

Causes:

- *Group A Streptococcus* (GAS) infection, especially pharyngitis.
- Autoimmune response where antibodies against streptococcal proteins cross-react with host tissues (molecular mimicry).

Clinical Features and Findings:

1. **Major Criteria (Jones Criteria)**
   - *Carditis*: Pancarditis with new murmurs (mitral/aortic regurgitation), pericarditis, or heart failure.
   - *Polyarthritis*: Migratory arthritis mainly affecting large joints.
   - *Chorea (Sydenham's chorea)*: Involuntary, rapid movements, emotional instability.
   - *Erythema marginatum*: Painless rash with ring-like borders.
   - *Subcutaneous nodules*: Firm, painless nodules over bony prominences.

2. **Minor Criteria:**
    - Fever (>38.5°C or >101.3°F)
    - Arthralgia (joint pain without swelling)
    - Elevated acute-phase reactants (ESR, CRP)
    - Prolonged PR interval on ECG

- **Definite RF diagnosis:**
    - Two major criteria
      OR
    - One major + two minor criteria, plus evidence of preceding group A streptococcal infection.

Investigations

- **Throat culture or rapid antigen test**: For group A streptococcus.
- **Antistreptolysin O (ASO) titre**: Raised titres suggest recent streptococcal infection.
- **CRP and ESR**: Elevated levels indicate inflammation.
- **ECG**: Prolonged PR interval, atrioventricular block.
- **Echocardiography**: Can reveal valvular abnormalities or myocarditis.

Management:

1. **Antibiotic Therapy:**
    - **Penicillin V**: 500 mg orally 2-3 times daily for 10 days (or 250 mg for children).
    - **Penicillin G benzathine**: 1.2 million units IM once (600,000 units in children).
    - **Erythromycin**: 250 mg 4 times daily for 10 days (alternative for penicillin allergy).
2. **Anti-inflammatory Therapy:**
    - **Aspirin**: 80–100 mg/kg/day divided every 4–6 hours (max 3–4 g/day), tapered over weeks as symptoms improve.
    - **Prednisolone**: 1–2 mg/kg/day in severe carditis.
3. **Heart Failure Management:**
    - Diuretics or ACE inhibitors as needed.
4. **Secondary Prophylaxis:**
    - **Benzathine penicillin G**: 1.2 million units IM every 3–4 weeks to prevent recurrent RF (5 years or until 21 years of age, whichever is longer).
    - **Oral penicillin V**: 250 mg twice daily for patients without access to IM therapy.

Infective endocarditis (IE)

Definition and Pathophysiology

- Infective endocarditis (IE) is a severe infection of the heart valves or endocardium caused by microorganisms (primarily bacteria).
- It develops when transient bacteremia interacts with damaged cardiac tissue, leading to vegetation formation (a mass of platelets, fibrin, microorganisms, and inflammatory cells). These vegetations make the infection hard to eliminate and may embolize, causing complications such as stroke or abscess formation.

Causes with Frequency

- **Staphylococcus aureus** (30-40%): Most common, often linked to intravenous drug use or prosthetic valve infections.
- **Streptococci species** (20-30%): Particularly Viridans streptococci and Streptococcus gallolyticus, commonly associated with dental infections.
- **Enterococci** (~10%): Typically linked to gastrointestinal or genitourinary infections.

- **HACEK organisms** (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella): Rare, culture-negative IE causes.
- **Fungal pathogens** (e.g., Candida spp.): Rare but severe, especially in immunocompromised patients.

Associations	Most common cause
Generally	*Staphylococcus aureus (coagulase positive)*
Prosthetic valves < 2 months post operative	*Staphylococcus epidermidis (coagulase negative)*
IV drug use	*Staphylococcus aureus*
Recent dental procedure	*Streptococcus viridans* : (*Streptococcus mitis* and *Streptococcus sanguinis*).
Colorectal cancer	*Streptococcus gallolyticus (formerly Streptococcus bovis):* **colonoscopy should be done**
Following bowel resection	***Bacteroides***
Culture negative + exposure to animals (sheep and cattle).	*Coxiella burnetiid* (Q fever agent), Brucella
Culture negative + exposure to cats	*Bartonella*
Culture negative + exposure to birds	Chlamydia psittaci
Culture negative + Human bite injury	**HACEK**: *(Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)*, **Gram negative bacteria**

Classification and Types

- **Native Valve Endocarditis (NVE):** Infection on a native heart valve.
- **Prosthetic Valve Endocarditis (PVE):** Occurs in individuals with prosthetic heart valves, classified as early (<12 months post-surgery) or late (>12 months).
- **Device-Related Endocarditis:** Associated with pacemakers or other intracardiac devices.
- **Right-Sided IE:** More common in intravenous drug users, affecting tricuspid valves.

Acute Endocarditis	Subacute Endocarditis
Larger vegetations	Smaller vegetations
Attacks previously normal valves	Attacks damaged or abnormal valves
Destructive; 50% mortality rate despite treatment	Less destructive; most patients recover with treatment
High-virulence organisms, especially *S aureus*	Low-virulence organisms, especially the viridans streptococci *S mutans* and *S sanguinis*

Diagnostic Criteria (Modified Duke Criteria)

- **Major Criteria:**
  1. Positive blood cultures from typical organisms.
  2. Evidence of endocardial involvement on echocardiography (e.g., vegetation or abscess).
- **Minor Criteria:**
  1. Predisposing factors (e.g., IV drug use, prosthetic valves).
  2. Fever ≥38°C.
  3. Vascular phenomena (e.g., arterial emboli).
  4. Immunological phenomena (e.g., Osler nodes, Roth spots).
  5. Microbiological evidence not meeting major criteria.
- **Definite IE:** 2 major OR 1 major + 3 minor OR 5 minor criteria.
- **Possible IE:** 1 major + 1 minor OR 3 minor criteria.

Clinical Features

- Fever, chills, and night sweats.
- New or changing heart murmurs.
- **Embolic phenomena:** Splinter hemorrhages, Janeway lesions, Osler nodes, and Roth spots.
- Severe cases may lead to stroke, renal infarction, or mycotic aneurysms.

Peripheral Signs Associated with Infective Endocarditis

Sign	Description
Janeway lesions	Non-tender, erythematous macular lesions on palms and soles, caused by septic microemboli.
Osler's nodes	Painful, red or purple, raised lesions on the pads of fingers and toes, associated with immune complex deposition.
Splinter haemorrhages	Thin, linear, reddish-brown streaks under the nails caused by small emboli or vasculitis.
Clubbing	Bulbous swelling of the distal phalanges, indicating long-standing endocarditis.
Roth spots	Retinal haemorrhages with pale centres, reflecting immune complex vasculitis.
Conjunctival petechiae	Small, painless haemorrhages in the conjunctiva, indicating microvascular involvement.
Petechiae	Small, red or purple spots on the skin, oral mucosa, or conjunctiva due to capillary haemorrhage.

Classical symptoms of infective endocarditis can be remembered using the mnemonic FROM JANE: fever, Roth spots, Osler nodes, murmur, Janeway lesions, anaemia, nail-bed haemorrhage, emboli.

Investigation

- **Transthoracic echocardiography (TTE) is the initial test of choice for all patients with suspected IE** → new or worsening valvular regurgitation, dehiscence of prosthetic valve, presence of vegetations. transesophageal echocardiogram (TEE) is preferred.
- **Blood cultures:**

- ⇨ If not critically ill; three sets of blood cultures drawn **>2 hours apart** from **different sites** before administration of antibiotics with repeat cultures in 48 to 72 hrs until bacterial clearance
- ⇨ **If critically ill, draw three sets of blood cultures over 1 hour prior to empiric therapy**

- **Consider serologies for Chlamydia, Q fever, Legionella, and Bartonella in "culture-negative" endocarditis.**
- **Urine routine:** Findings related to secondary system involvement → RBC casts, Microscopic hematuria, proteinuria, pyuria
- **CBC:** Normochromic normocytic anemia, Leukocytosis
- **Inflammatory markers:** ↑ **CRP,** ↑ **ESR**
- **RF: +ve**
- **Decreased C3, C4**
- **ECG:** atrioventricular block→ paravalvular involvement (**Aortic valve endocarditis can cause aortic root abscess which can cause damage to the AV node resulting in prolongation of the PR interval on ECG.**)
- **Chest x-ray:** may reveal evidence of septic pulmonary emboli or congestive heart failure

Complications

- Heart failure, stroke, embolism, mycotic aneurysm, and abscess formation.
- Persistent bacteremia and renal dysfunction.

Management

1. **Antibiotic Therapy:**
   - Empiric therapy often includes **vancomycin** combined with a beta-lactam (e.g., ceftriaxone).
   - **Duration:** NVE: 2-6 weeks; PVE: ≥6 weeks.
   - **Specific regimens:**
     - Vancomycin 15-20 mg/kg IV every 8-12 hours.
     - Ceftriaxone 2 g IV daily.
     - Add rifampin for prosthetic valve infections.
     - Fungal IE requires **amphotericin B** or **echinocandins**.
2. **Surgical Intervention:**
   - Indicated in severe cases with valve dysfunction, uncontrolled infection, or large vegetations (>10 mm).
   - Surgery may involve valve replacement or debridement of infected tissue.
3. **Supportive Measures:**
   - Manage heart failure and embolic complications.
   - Anticoagulation is typically avoided unless indicated (e.g., mechanical valves without active bleeding).
4. **Prophylaxis:** Antibiotic prophylaxis for high-risk patients undergoing dental procedures to prevent IE.

Antibiotics recommendation

Scenario	Suggested antibiotic therapy
Initial blind therapy	• Native valve: ⇨ Not allergic to penicillin , no MRSA , not sever sepsis → Amoxicillin + gentamicin ⇨ Allergic to penicillin , MRSA , or sever sepsis → vancomycin + gentamicin • Prosthetic valve → vancomycin + rifampicin + gentamicin
Staphylococci endocarditis	• Native valve: ⇨ Not allergic to penicillin , no MRSA , not sever sepsis → Flucloxacillin ⇨ Allergic to penicillin , MRSA , or sever sepsis → Vancomycin + rifampicin • Prosthetic valve: ⇨ Not allergic to penicillin , no MRSA , not sever sepsis → Flucloxacillin + rifampicin + gentamicin ⇨ Allergic to penicillin , MRSA , or sever sepsis → vancomycin + rifampicin + gentamicin
Streptococci endocarditis	• Native valve **and** Prosthetic valve : ⇨ Not allergic to penicillin → Benzylpenicillin ± gentamicin ⇨ Allergic to penicillin → Vancomycin + gentamicin

Prophylaxis recommendations for infective endocarditis

Condition Requiring Prophylaxis	Examples	Procedures Requiring Prophylaxis	Recommended Prophylaxis Regimen
High-risk cardiac conditions	- Prosthetic heart valves - Previous infective endocarditis - Congenital heart disease (e.g., unrepaired cyanotic heart defects)	- Dental procedures involving manipulation of the gums or periapical region of teeth - Procedures involving infected skin or musculoskeletal tissue	**Amoxicillin 2 g orally 1 hour before procedure** **If allergic to penicillin**: Clindamycin 600 mg or Azithromycin 500 mg
Moderate-risk conditions (discretionary use)	- Valve repair without prosthetic material - Certain congenital heart defects	Dental procedures with extensive tissue manipulation	Same as above, but the need for prophylaxis varies by patient
No prophylaxis required	- Pacemaker insertion - Routine GI or GU procedures (unless infected tissues are present)	- Diagnostic procedures like colonoscopy or cystoscopy	None recommended unless active infection present

Myocarditis

Definition:

- Inflammation of the myocardium in the absence of predominant acute or chronic ischaemia.

Pathology:

- Inflammatory infiltrates with focal necrosis of myocardial tissue.

Causes

1. **Idiopathic:**
    - No cause identified in 50% of cases.
2. **Infectious:**
    - **Viral:**
        - *Adults*: Parvovirus B19, Human herpesvirus 6.
        - *Children*: Coxsackie B virus (associated with dilated cardiomyopathy).
        - Others: HIV, Hepatitis C, Influenza, Epstein-Barr virus.
    - **Bacteria:** Diphtheria, Clostridia.
    - **Spirochetes:** Lyme disease (often presents with heart block).
    - **Protozoa:**
        - Chagas disease (causes dilated cardiomyopathy).
        - Toxoplasmosis.
3. **Non-infectious:**
    - Autoimmune: Lupus, Sarcoidosis, Dermatomyositis, Polymyositis.
    - Vasculitis: Kawasaki disease.
    - Toxins: Carbon monoxide, black widow venom, cocaine.
    - Medications: Sulfonamides, anthracycline chemotherapy (e.g., doxorubicin).
    - Radiation therapy.

Presentation

- Young patient with a **viral prodrome** (fever, myalgia, respiratory symptoms).
- **Heart failure symptoms:** Dyspnea, orthopnea, leg swelling.
- **Chest pain** due to pericardial involvement.
- **Palpitations:** Often sinus tachycardia.

Investigations

- **Troponin:** Significantly elevated.
- **ESR/CRP:** Raised inflammatory markers.
- **ECG:**
    - Sinus tachycardia or ventricular arrhythmias.
    - Nonspecific ST changes or diffuse ST elevation (perimyocarditis).
- **Echocardiography:** Global systolic dysfunction.
- **Cardiac MRI (CMR):** Supports the diagnosis of myocarditis.
- **Endomyocardial biopsy (EMB):** Definitive test using Dallas criteria.
    - *Active myocarditis*: Inflammatory infiltrate with myocardial necrosis.
    - *Borderline myocarditis*: Inflammation without myocardial necrosis.

Differential Diagnosis

- **Acute coronary syndrome (ACS):** May mimic myocarditis with ECG changes and increased troponins.

Treatment

- **Supportive care:** Manage as heart failure.
- **Immunosuppressive therapy**: For autoimmune causes (e.g., lupus myocarditis).
- **NSAIDs:** Avoid in the acute phase to prevent impaired healing.

Heart failure

Heart failure: Causes and diagnosis

Aspect	Details
Definition	Structural or functional impairment of ventricular filling/ejection, affecting cardiac output.
Mechanism	Cardiac output depends on preload, afterload, and ventricular contractility.
Key Causes	Ischaemic heart disease, hypertension, valvular disease, arrhythmias, myocarditis, tamponade, cardiomyopathy, renal failure, alcohol abuse, high output states (e.g., anemia, hyperthyroidism).
Types	**HFrEF**: Reduced EF ≤ 35–40%, decreased contractility. Causes: MI, cardiomyopathy, high output failure. **HFpEF**: Preserved EF ≥ 40–50%, impaired relaxation, increased stiffness. Causes: Hypertension, restrictive cardiomyopathy, pericarditis.
Features	**Fluid Overload**: Orthopnoea, raised JVP, pulmonary crackles, oedema, ascites. **Low Output**: Tachycardia, hypotension, confusion, poor capillary refill, oliguria.
NYHA Classification	**Class I**: No symptoms **Class II**: Symptoms with moderate exertion **Class III**: Symptoms with daily activities **Class IV**: Symptoms at rest
ACC/AHA Staging	**A**: High risk, no structural heart disease. **B**: Structural disease, no symptoms. **C**: Structural disease with symptoms. **D**: Refractory end-stage heart failure.
Complications	Cardiorenal syndrome, pulmonary congestion, arrhythmias, sepsis, thromboembolism.
Key Diagnostic Tests	**Echocardiogram**: Assess ejection fraction, valve function. **BNP Levels**: Elevated in heart failure (rule out if BNP < 100 pg/ml). **CXR**: Cardiomegaly, pulmonary oedema, Kerley B lines.
BNP Interpretation	**High BNP**: >400 pg/ml (poor prognosis). **Normal BNP**: <100 pg/ml (excludes acute heart failure).
Chest X-ray Signs	Cardiomegaly, pulmonary oedema, Kerley B lines, pleural effusion.
Investigations	Blood tests (BNP, CBC, electrolytes), echocardiogram, chest X-ray, ECG, cardiac MRI if necessary.
Diagnosis Strategy	For patients without prior MI: - If BNP >400 → Echocardiogram within 2 weeks - If BNP 100–400 → Echocardiogram within 6 weeks
BNP Modifying Factors	**Increase BNP**: LVH, ischaemia, AF, COPD. **Decrease BNP**: Obesity, diuretics, ACE inhibitors, African ethnicity.

Typical CXR signs associated with heart failure

B-type (Brain) Natriuretic Peptide (BNP)

Parameter	Details
Definition	BNP is a **hormone released by the ventricles** in response to **ventricular stretch** and **volume overload.**
Physiological Role	Promotes **vasodilation, natriuresis,** and **diuresis**, reducing **preload** and **afterload.**
BNP vs. NT-proBNP	- **BNP:** Active form of the peptide. - **NT-proBNP:** Inactive precursor, more stable and used in clinical practice.
Indications for Testing	- Diagnosis and monitoring of **heart failure.** - Differentiating **dyspnea** due to heart failure from other causes (e.g., COPD).
Normal Range	- BNP: **<100 pg/mL** - NT-proBNP: Age-based ranges (e.g., **<125 pg/mL** for <75 years).
Clinical Significance	- **Elevated BNP/NT-proBNP:** Suggests **heart failure** or other conditions with ventricular strain (e.g., pulmonary hypertension). - **Low BNP:** Makes heart failure less likely.
Causes of Elevated BNP	- **Heart failure** (both systolic and diastolic) - **Acute coronary syndrome** - **Pulmonary hypertension** - **Valvular heart disease** - Chronic kidney disease (reduced clearance).
Factors Affecting BNP Levels	- **Increased:** Age, renal impairment, atrial fibrillation. - **Decreased:** Obesity, certain medications (e.g., ACE inhibitors, ARBs).

Parameter	Details
Clinical Use	- Assessing **severity of heart failure.** - **Monitoring response** to heart failure treatment. - Predicting **prognosis** in heart failure and acute coronary syndromes.
Limitations	- BNP levels may be **nonspecific** (affected by renal function, age). - Less reliable in **obese patients.**

Heart Failure: Management

Category	Details
Identify and Treat Causes	Non-compliance, uncontrolled hypertension, arrhythmias, MI, fluid overload, pulmonary infection, anemia, inappropriate medications (e.g., NSAIDs), endocrine disorders (e.g., thyrotoxicosis)
Pharmacological Management	**Acute HF:** - **Oxygen:** Aim SpO2 >95% (or >90% in COPD) - **IV Loop Diuretics:** Furosemide 40–120 mg IV (can increase in resistance cases) - **IV Nitrates:** If BP >95 mmHg - **ACE Inhibitors/ARBs:** Titrate every 2 weeks, monitor electrolytes and renal function - **Thiazides & Aldosterone Antagonists:** Add if diuretic resistance (e.g., spironolactone 25–50 mg/day)
Diuretics & β-Blockers Use	- Continue β-blockers unless HR <50 bpm or AV block - Increase diuretics in acute decompensation; reintroduce β-blockers post-stabilization
Digoxin	Useful in persistent symptoms or atrial fibrillation. Dose: 62.5–125 mcg/day
Management of Hyponatraemia	Water restriction; furosemide reduction may not be feasible in volume overload
Non-Pharmacological Management	- Non-invasive ventilation (e.g., CPAP) - Fluid restriction: 1.5–2 L/day - Sodium restriction: ≤1.5 g/day - Exercise training; smoking cessation
Supportive Care	Vaccinations (Influenza annually, pneumococcal one-off or 5-yearly with CKD); management of hypertension, diabetes, and dyslipidemia
Advanced Interventions	**Implantable Cardioverter Defibrillator (ICD):** If LVEF ≤35% with NYHA class II–III **Cardiac Resynchronization Therapy (CRT):** If QRS >150 ms or mechanical dyssynchrony confirmed via echocardiography
Drug Classes with Prognostic Benefit	1. Beta-blockers 2. ACE inhibitors/ARBs 3. Aldosterone antagonists 4. Hydralazine + Nitrates 5. ARNIs (e.g., valsartan-sacubitril)
Iron Deficiency Treatment	IV iron for patients with HF and iron deficiency

Mechanical Support & Transplant	- Mechanical Circulatory Support (MCS) in end-stage HF - Cardiac transplant in suitable candidates
Avoidance of Contraindicated Drugs	- Avoid calcium channel blockers (except amlodipine) - NSAIDs - Pioglitazone and other thiazolidinediones - Non-dihydropyridine calcium channel blockers with β-blockers (risk of complete heart block)

Potentially harmful drugs to avoid in heart failure

Drug to avoid	Notes
Non-steroidal anti-inflammatory drugs (NSAIDs)	• May cause sodium and water retention, peripheral vasoconstriction, worsen heart failure, and decrease renal function. • Acute renal failure may be more likely when these agents are used in combination with an ACE inhibitor (ACEI) / angiotensin receptor blocker (ARB) and/or diuretic.
Non-dihydropyridine calcium channel blockers –verapamil and diltiazem1	• Negative inotropic effect may further depress cardiac function. Risk is greatest with verapamil, then diltiazem and least risk with dihydropyridines, but use with caution • Non-dihydropyridine calcium channel blockers are contraindicated in systolic heart failure , but may be useful in heart failure with preserved ejection fraction where slowing heart rate can increase filling time
Tricyclic antidepressants	May prolong QT interval and cause arrhythmias as well as hypotension from alpha-blocking effects
Thiazolidinediones (e.g. pioglitazone)	May cause fluid retention and heart failure by increasing renal sodium reabsorption
Corticosteroids	May worsen heart failure due to sodium and water retention (mineralocorticoid effect)
Clozapine	May cause cardiomyopathy and myocarditis
Oncology treatments such as anthracyclines (doxorubicin, daunorubicin), trastuzumab	may cause heart failure
Tumour necrosis factor antagonists (e.g. infliximab, etanercept)	May cause heart failure
Moxonidine (centrally acting antihypertensive)	Contraindicated in heart failure. Associated with increased mortality in heart failure

Types of Cardiomyopathies

Type	Definition	Causes	Diagnostic Features
Dilated Cardiomyopathy (DCM)	Progressive dilation and impaired contraction of the left or both ventricles.	**Idiopathic**, genetic mutations, alcohol, myocarditis, chemotherapy (doxorubicin), and infections (HIV, coxsackievirus).	**Echocardiogram:** LV dilation and systolic dysfunction with reduced ejection fraction (HFrEF). **MRI:** Late gadolinium enhancement in non-ischemic patterns.
Hypertrophic Cardiomyopathy (HCM)	Thickened, stiff ventricular wall, often of the left ventricle, with no dilatation.	Genetic mutations (sarcomere proteins), familial cases, autosomal dominant inheritance.	**Echocardiogram:** Asymmetrical LV hypertrophy, often involving the septum. **ECG:** LV hypertrophy with deep T-wave inversions. Systolic anterior motion (SAM) of mitral valve.
Restrictive Cardiomyopathy (RCM)	Impaired filling of the ventricles due to rigid walls without hypertrophy.	Amyloidosis, sarcoidosis, hemochromatosis, post-radiation fibrosis, endomyocardial fibrosis.	**Echocardiogram:** Normal EF but impaired diastolic filling. **MRI:** Diffuse enhancement typical of amyloidosis or sarcoidosis.
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	Fibrofatty replacement of right ventricular myocardium, leading to arrhythmias.	Genetic mutations (desmosomal proteins) with autosomal dominant inheritance, sports-related.	**MRI:** Fatty infiltration of RV. **ECG:** T-wave inversions in V1-V3, epsilon waves. **Biopsy:** Fibrofatty replacement of myocardium.
Takotsubo Cardiomyopathy (Stress-Induced)	Transient LV dysfunction triggered by acute stress, often mimicking an acute MI.	Acute emotional or physical stress (e.g., loss of loved one), catecholamine surge.	**Coronary Angiography:** Normal arteries with apical ballooning. **Echocardiogram:** Transient apical dyskinesia and basal hyperkinesia.
Ischemic Cardiomyopathy	Chronic systolic dysfunction due to coronary artery disease.	Myocardial infarction, chronic ischemia from coronary artery disease.	**Echocardiogram:** Regional wall motion abnormalities. **Angiography:** Coronary stenosis or blockage.
Peripartum Cardiomyopathy	Dilated cardiomyopathy occurring in late pregnancy or postpartum period.	Unknown; risk factors include multiple pregnancies, advanced maternal age, preeclampsia.	**Echocardiogram:** LV dilatation with reduced EF. **MRI:** No ischemic pattern of fibrosis.

Hypertrophic obstructive cardiomyopathy (HOCM)

Definition

- **Hypertrophic Obstructive Cardiomyopathy (HOCM)** is a genetic cardiac disorder characterized by thickening of the heart muscle, particularly the interventricular septum. This thickened muscle obstructs the outflow of blood from the left ventricle during contraction, leading to impaired cardiac function.

Pathophysiology

- **Autosomal dominant disorder** of the muscle caused by mutations in contractile protein genes (e.g., β-myosin heavy chain, myosin binding protein C).
- Septal hypertrophy → *left ventricular outflow tract (LVOT) obstruction* → arrhythmias, sudden death.

Prevalence

- 1 in 500 individuals.
- ***HOCM is the most common cause of sudden cardiac death in the young***

Clinical Features

- **Asymptomatic:** Often discovered incidentally on echocardiography.
- **Symptomatic:**
  - *Dyspnoea* (most common symptom), angina, syncope.
  - Jerky pulse, double apex beat.
  - Ejection systolic murmur: *Increases* with Valsalva manoeuvre, *decreases* on squatting.
  - Prominent 'a' wave in JVP.
  - *Sudden cardiac death*: Due to ventricular arrhythmias.
  - *Association:* Wolff-Parkinson-White syndrome, Friedreich's ataxia.

Investigations

- **Echocardiography** (Key mnemonic: MR SAM ASH):
  - *Mitral Regurgitation (MR)*
  - *Systolic Anterior Motion (SAM)* of the mitral valve
  - *Asymmetric Septal Hypertrophy (ASH)*
- **ECG findings:**
  - Left ventricular hypertrophy, progressive T-wave inversion.
  - Dagger-like Q waves, right/left axis deviation, PR prolongation.
  - Atrial fibrillation, right bundle branch block (most common ECG indicator).

Management

- **Pharmacological Treatment:**
  - **Beta-blockers** (first-line): ↑ diastolic filling, ↓ contractility, ↓ gradient.
  - **Disopyramide** (Class IA antiarrhythmic) if beta-blockers are ineffective – monitor for QT prolongation.
  - **Verapamil**: Second-line (avoid in Wolff-Parkinson-White syndrome).
  - **Contraindicated drugs:** Vasodilators (e.g., nitrates, ACE inhibitors), digoxin – may exacerbate LVOT obstruction.
- **Preventing Sudden Cardiac Death:**
  - **ICD (Implantable Cardioverter Defibrillator)**: Indicated for survivors of cardiac arrest or those with sustained VT causing syncope.

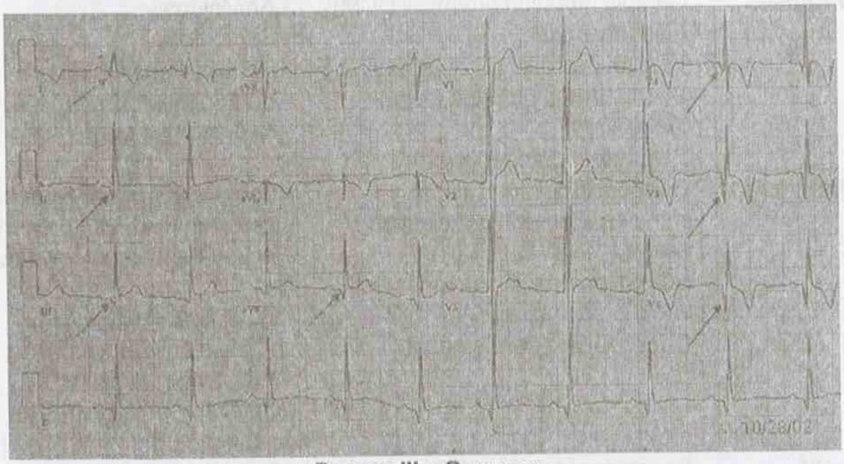
- **Invasive Treatments:**
    - *Ventricular septal myectomy* or *alcohol septal ablation* if LVOT gradient ≥50 mmHg and symptoms persist despite therapy.

Family Screening

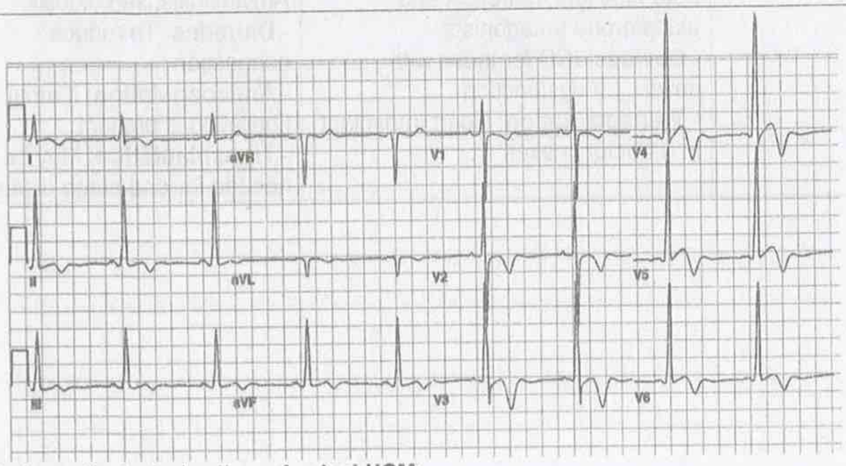
- **ECG** and **transthoracic echocardiography (TTE)** are recommended.
- Genetic testing is not routinely advised.

Poor Prognostic Indicators

- Syncope, family history of sudden death.
- Maximum left ventricular wall thickness >3 cm.
- Non-sustained VT on Holter monitoring.
- Young age at presentation.
- Blood pressure drop during peak exercise.



Dagger-like Q waves



This ECG shows the typical pattern of **apical HCM**:

- Large precordial voltages.
- Giant T wave inversions in the precordial leads
- Inverted T waves are also seen in the inferior and lateral leads.

Comparison between Dilated Cardiomyopathy (DCM) and Restrictive Cardiomyopathy (RCM):

Feature	Dilated Cardiomyopathy (DCM)	Restrictive Cardiomyopathy (RCM)
Definition	DCM is characterized by dilatation of the heart chambers, particularly the left ventricle, leading to systolic dysfunction.	RCM is marked by impaired ventricular filling due to stiff myocardium, with preserved systolic function.
Pathophysiology	Reduced ventricular contractility leads to decreased ejection fraction, ventricular dilatation, and heart failure.	The stiff myocardium prevents proper filling during diastole, leading to elevated diastolic pressures.
Common Causes	- Genetic mutations (familial DCM) - Alcohol abuse - Viral myocarditis (Coxsackievirus) - Chemotherapy agents (e.g., doxorubicin) - Peripartum cardiomyopathy	- Amyloidosis - Sarcoidosis - Hemochromatosis - Endomyocardial fibrosis - Radiation therapy
Unique Diagnostic Features	- **Echocardiogram**: Dilated ventricles with reduced ejection fraction - **ECG**: Non-specific changes, left bundle branch block - **Chest X-ray**: Cardiomegaly	- **Echocardiogram**: Normal-sized ventricles with preserved ejection fraction but impaired filling - **ECG**: Low-voltage QRS complexes (in amyloidosis) - **MRI**: Late gadolinium enhancement in infiltrative diseases
Management	- **Pharmacological**: ACE inhibitors, beta-blockers, diuretics, and aldosterone antagonists - **Devices**: ICD for those with severe LV dysfunction - **Transplantation**: Heart transplant in refractory cases	- **Treat underlying cause**: Amyloidosis, sarcoidosis - **Diuretics**: To reduce congestion - **Anticoagulation**: If atrial fibrillation is present - **Transplantation**: May be needed for end-stage disease

Peripartum cardiomyopathy (PCM)

Condition	Details
Peripartum Cardiomyopathy (PCM)	**Definition:** A dilated cardiomyopathy that develops in the last month of pregnancy or within 6 months postpartum without pre-existing heart disease. **Risk Factors:** Young or advanced maternal age, twin pregnancy, hypertension, multiparity, African descent. **Management:** Optimising heart failure treatment with diuretics, vasodilators, and beta-blockers. ACE inhibitors are only used postpartum. Anticoagulation (heparin) is advised to prevent thromboembolism. **Prognosis:** 50% of patients experience persistent LV dysfunction, with a significant recurrence risk in future pregnancies.
Tocolysis-associated Pulmonary Oedema	**Cause:** Use of tocolytic agents like beta-agonists (e.g., terbutaline) to prevent preterm labour. Concomitant corticosteroid use increases the risk. **Pathophysiology:** Fluid overload, with possible cardiac dysfunction and capillary leakage. **Investigation:** Chest X-ray reveals pulmonary infiltrates without cardiomegaly. **Treatment:** Discontinue tocolytics, provide oxygen, and manage fluid balance. **Differential:** PCM presents later in pregnancy or postpartum and shows cardiomegaly on imaging.

Takotsubo cardiomyopathy

Definition: A type of non-ischaemic cardiomyopathy associated with a transient, apical ballooning of the myocardium. Acute, stress-induced, reversible dysfunction of the left ventricle

Epidemiology: especially postmenopausal women > 60 years

Pathophysiology: emotional/physical stress → massive catecholamine discharge → cardiotoxicity, multi-vessel spasms and dysfunction → myocardial stunning

Features

- Chest pain → (ST elevation with normal coronary angiogram)
- Features of heart failure

Treatment: supportive

Prognosis: spontaneous recovery if stressors are avoided

Congenital heart disease

Congenital heart disease: types

Type	Examples	Description and Key Points
Acyanotic	- **Ventricular Septal Defect (VSD)** - **Atrial Septal Defect (ASD)** - **Patent Ductus Arteriosus (PDA)** - **Coarctation of the Aorta** - **Aortic Valve Stenosis**	- **VSD**: Most common, accounting for 30% of congenital heart disease. - **ASD**: 10% prevalence. - **PDA**: Persistence of fetal ductus arteriosus after birth. - **Coarctation**: Narrowing of the aorta, often near the ductus arteriosus. - **Aortic Stenosis**: Obstruction of blood flow from the left ventricle.
Cyanotic	- **Tetralogy of Fallot (TOF)** - **Transposition of the Great Arteries (TGA)** - **Tricuspid Atresia** - **Pulmonary Valve Stenosis** - **Total Anomalous Pulmonary Venous Connection (TAPVC)**	- **TGA**: The most common cyanotic defect at birth; treated with prostaglandins to keep the ductus arteriosus patent for oxygenated blood flow. - **Tetralogy of Fallot**: Most common cyanotic heart defect presenting later (1–2 months). - **TAPVC**: All four pulmonary veins drain into the right atrium, causing systemic and pulmonary blood to mix.

Tetralogy of Fallot (TOF)

Prevalence

- TOF is the most common cause of cyanotic congenital heart disease. generally present at around 1-2 months (transposition of the great arteries is the more common lesion at birth)
- It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old

Features

- TOF is a result of anterior malalignment of the aorticopulmonary septum. The four characteristic features are:
  1. ventricular septal defect (VSD)
  2. right ventricular hypertrophy
  3. right ventricular outflow tract obstruction, pulmonary stenosis. There is a single sound in Fallot's because of an absent P2.
  4. overriding aorta
- Cyanosis (right-to-left shunt)

- **Ejection systolic murmur** due to pulmonary stenosis (the VSD doesn't usually cause a murmur)
- **Chest x-ray** shows a 'boot-shaped' heart
- **ECG** shows right ventricular hypertrophy

Management

- surgical repair is often undertaken in two parts
- cyanotic episodes may be helped by beta-blockers to reduce infundibular spasm

Ventricular septal defects (VSD)

VSDs are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later

Prevalence

- The second most common congenital heart defect (bicuspid aortic valve is the most common congenital heart defect)
- **The most common site for a VSD → Peri-membranous** (70-80% of VSDs and are situated between the inlet and outlet portions of the septum).

Associations

- Congenital VSDs: associated with chromosomal disorders (e.g. Down's syndrome, Edward's syndrome, Patau syndrome)
- Non-congenital causes :
  - ⇨ Fetal alcohol syndrome
  - ⇨ Intrauterine infection (e.g., TORCH)
  - ⇨ post myocardial infarction

Features

- Pan-systolic murmur : louder in smaller defects, **loudest at the left lower sternal edge (LSE)**
- Mid-diastolic murmur over cardiac apex: Due to increased flow through the mitral valve
- Systolic thrill
- Loud pulmonic S2 (if pulmonary hypertension develops)

Investigations

- Chest x-ray: Enhanced pulmonary vascular markings, Left atrial and ventricular enlargement
- ECG → Biventricular hypertrophy (**biphasic QRS complexes in V2–5** – which is known as the **Katz Wachtel phenomenon** and is **classic for VSD**).
- Doppler echocardiography: confirms diagnosis

Complications

- Aortic regurgitation: poorly supported right coronary cusp → cusp prolapse → AR
- Infective endocarditis
- **Pulmonary hypertension:** pregnancy is contraindicated in women with pulmonary hypertension as it carries a 30-50% risk of mortality.
- Right heart failure
- Eisenmenger's complex

Treatment

- Small to moderate defects → often heal spontaneously (in 50% of cases)
- Symptomatic and large VSDs → Surgical (patch) repair
- If Eisenmenger's occurred → Heart-lung transplant or lung transplant with concurrent VSD repair

Atrial Septal Defect (ASD)

Prevalence

- ASD is a **common congenital heart defect**, though **ventricular septal defect (VSD)** is more prevalent.

Types of ASD

Type	Key Features	ECG Findings
Ostium Primum	- Presents **earlier** than ostium secundum defects. - Associated with **abnormal AV valves.** - AV node is **displaced posteriorly and inferiorly,** causing **delayed conduction.** - Associated with **Holt-Oram syndrome** (tri-phalangeal thumbs).	**RBBB** with **LAD,** prolonged PR interval
Ostium Secundum	- The **most common ASD** (70%). - Associated with **Holt-Oram syndrome.**	**RBBB** with **RAD**

Clinical Tip:

- **Wide, fixed split-second heart sound + RAD → Ostium Secundum.**
- **Wide, fixed split-second heart sound + LAD → Ostium Primum.**

Symptoms:

- Often **asymptomatic** in childhood, frequently detected during routine health exams.
- **Mild fatigue.**
- **Frequent respiratory infections.**
- Larger defects can lead to **right ventricular failure,** causing **shortness of breath.**

Physical Examination:

- **Mid-systolic ejection murmur** at the **left second intercostal space (ICS)** due to increased pulmonary flow.
- **Soft mid-diastolic murmur** over the **lower left sternal border** from increased flow across the tricuspid valve.
- **Loud S1.**
- **Wide, fixed split of S2** that does not vary with respiration.
- **Heaving cardiac impulse** at the lower left sternal border (LLSB).

Complications

- **Congestive Heart Failure (CHF):** Develops in the 2nd or 3rd decade of life.
- **Eisenmenger's Syndrome:** Pulmonary hypertension leads to right ventricular hypertrophy and reversal to a **right-to-left shunt.**
- **Stroke:** Due to **paradoxical embolus** through the defect.

Associated Conditions

- **Tricuspid atresia:** ASD is often present.
- **Down syndrome.**
- **Fetal alcohol syndrome.**
- **Holt-Oram syndrome (hand-heart syndrome):** Autosomal dominant disorder with:
    - **ASD**
    - **First-degree heart block**
    - **Upper limb abnormalities** (e.g., absent radial bones)
    - Affects ~1 in 100,000 children.

Investigations

- **Doppler Echocardiography:** Confirms diagnosis.
- **ECG Findings:**
    - **Right bundle branch block (RBBB)** with **rSR' pattern** in right precordial leads.
    - **Axis deviation:**
        - Ostium primum → **Left axis deviation** (LAD).
        - Ostium secundum → **Right axis deviation** (RAD).
    - **First-degree heart block** (prolonged PR interval).
- **Chest X-ray:**
    - Enlarged **right atrium**, **right ventricle**, and **main pulmonary artery**.
- **DLCO:** Grossly elevated due to left-to-right shunting and increased pulmonary blood flow.

Clinical Tip for Diagnosis

- **Prominent left precordium** in a young patient with an **ejection murmur** in the **second left ICS** indicates **ASD with pulmonary hypertension**.

Patent ductus arteriosus (PDA)

Definition

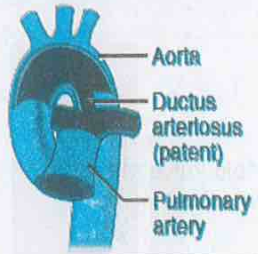
- A cyanotic congenital heart defect (connection between the pulmonary trunk and descending aorta). More common in premature babies, born at high altitude or maternal rubella infection in the first trimester

Features

- Left subclavicular thrill
- Continuous 'machinery' murmur at the left upper sternal edge with late systolic accentuation
- Large volume, bounding, collapsing pulse
- Wide pulse pressure
- Heaving apex beat

Management

- Indomethacin closes the connection in the majority of cases
- If associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair



"Endomethacin" (indomethacin) ends patency of PDA; PGE kEEps it open (may be necessary to sustain life in conditions such as transposition of the great vessels).

PDA is normal in utero and normally closes only after birth.

Patent foramen ovale (PFO)

Prevalence: PFO is **present in around 20% of the population**.

Complications

- **Paradoxical embolisation:** thrombus pass from the right-to-left side of the heart (e.g. DVT cause a stroke) (may be caused also by ASD but much less common than PFO)
- **Migraine:** Some studies have reported improvement in migraine symptoms following closure of the PFO

Investigations

- Right heart catheter: left to right shunting of oxygenated blood at level of the atrium. oxygen saturation data show a step-up in the saturations between the vena cava and the right atrium.

> Paradoxical embolus - PFO most common cause - do TOE

Eisenmenger's syndrome

> **Eisenmenger's syndrome - the reversal of a left-to-right shunt**

Pathophysiology

- Reversal of a left-to-right shunt in a congenital heart defect due to pulmonary hypertension.
- Uncorrected left-to-right shunt (VSD, ASD, PDA) → remodeling of the pulmonary microvasculature → obstruction to pulmonary blood and pulmonary hypertension → **Eisenmenger's syndrome**

Features

- Cyanosis
- Right ventricular failure
- Original murmur may disappear
- Clubbing
- Polycythemia
- Haemoptysis, embolism

Management: heart-lung transplantation

Ebstein's anomaly

Definition

- A congenital heart defect characterised by low insertion of the tricuspid valve resulting in a **large atrium and small ventricle (atrialisation of the right ventricle)**. May be caused by exposure to lithium in-utero.

Features

- Hypoplastic (atrialised) RV
- Apical displacement of the septal and posterior tricuspid valve leaflets
- ASD
- **Right bundle branch block pattern on ECG.**

Associations

- Tricuspid incompetence (pan-systolic murmur, giant V waves in JVP)
- Wolff-Parkinson White syndrome occurs in around 15% of the patients.

The presence of delta waves and short PR interval is indicative of WPW. When correlated with past surgical history (repair of atrial septal defect and tricuspid valve abnormalities as a child), Ebstein's anomaly is the most likely diagnosis.

Dextrocardia

Definition: The heart is located on the right side of the chest.

- **Situs solitus (isolated dextrocardia)**: dextrocardia with normal position of other thoracoabdominal structures. benign condition, typically, patients have a normal life expectancy
- **Situs inversus totalis** (reversal in the position of other organs)
- **Kartagener syndrome:** classic triad of situs inversus (reversal in the position of the abdominal organs), recurrent sinusitis, and bronchiectasis

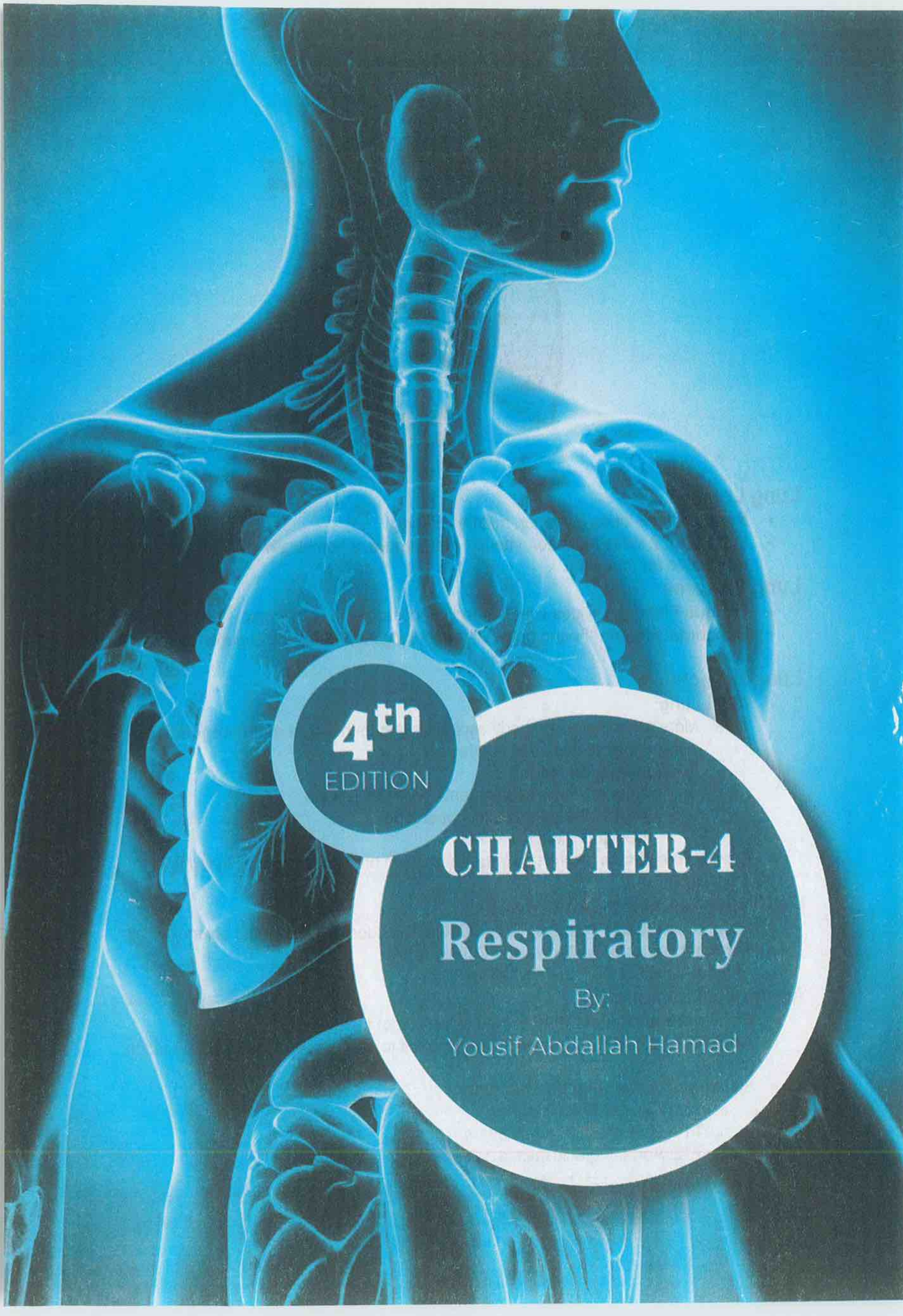
ECG Features

- Right axis deviation
- Negative P wave and QRS complex in lead I.
- Upright p wave in AVL
- Reverse R wave progression across the precordium; the R wave is tallest in V1 and progressively decreases in amplitude in leads V2 to V6. The diagnosis may be confirmed by obtaining right-sided chest leads that demonstrate the normal progression of R wave amplitude

*Characteristic changes of dextrocardia include a **negative P wave and QRS complex in lead 1**, since atrial and ventricular depolarization begin on the left and spread to the right. There is also **reverse R wave progression** across the precordium; **the R wave is tallest in V1, and progressively decreases in amplitude in leads V2 to V6**.*

Cardiac dextroposition: heart is displaced to the right side as a result of extracardiac causes, such as a diaphragmatic hernia, right pneumonectomy, or right lung hypoplasia.

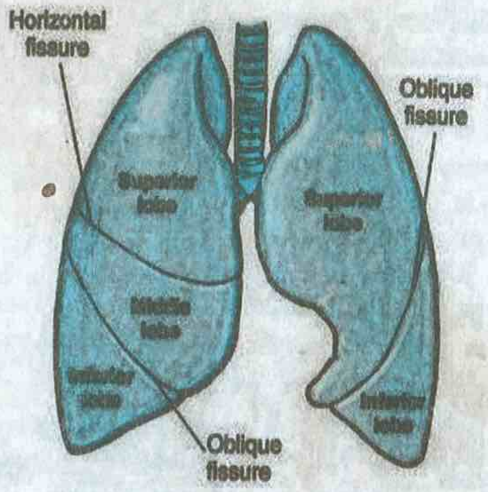
THIS PAGE INTENTIONALLY LEFT BLANK



CHAPTER-4
Respiratory

By:

Yousif Abdallah Hamad



Lung Anatomy

Lung Lobes

- **Right Lung**: 3 lobes (superior, middle, inferior).
- **Left Lung**: 2 lobes (superior, inferior) and **lingula**, a homolog of the right middle lobe, with space for the heart.

Lung Fissures

- **Oblique Fissure**: Divides superior and inferior lobes in both lungs.
- **Horizontal Fissure**: Found only in the right lung, separates the superior and middle lobes.

Lung Bronchi

- **Right Lung**:
  - More prone to foreign body aspiration due to the **right main bronchus** being wider, more vertical, and shorter.
  - **Foreign body location**:
    - **Supine**: Superior segment of right lower lobe.
    - **Right side lying**: Right upper lobe.
    - **Upright**: Right lower lobe.
- **Airway Resistance**: Highest in large-to-medium bronchi and lowest in terminal bronchioles.

Cell Types in the Respiratory Zone

- **Bronchi and Early Terminal Bronchioles**: Pseudostratified ciliated columnar cells.
- **Terminal Bronchioles Onwards**: Cuboidal cells.
- **Alveoli**: Simple squamous epithelium.

Anatomical Landmarks

- **Cartilage and Goblet Cells**: Extend to the end of the bronchi.
- **Angle of Louis (Sternal Angle)**: Corresponds to T4/T5; site of tracheal bifurcation (carina).
- **Structures Perforating the Diaphragm**:
  - **T8**: IVC, right phrenic nerve.
  - **T10**: Oesophagus, vagus nerve.
  - **T12**: Aorta, thoracic duct, azygos vein.

- **Tracheal Bifurcation**: At T4 ("bi-four-cates at 4").
- **Diaphragm Innervation**: C3, C4, C5 (phrenic nerve).
  - Pain referred to **shoulder (C5)** and **trapezius ridge (C3, C4)**.

Azygos Lobe of the Lung

- **Normal Variant**: Found in ~0.5% of chest X-rays.
- **Formation**: Displaced azygos vein creates a pleural fissure into the right upper lobe.
- **Appearance**: Seen as a "reverse comma sign" on imaging.
- **Embryology**: Formed when the posterior cardinal vein fails to migrate over the apex.

Clinical Tips

1. **Foreign Body Aspiration**:
   - More common in the **right lung** due to the bronchus' anatomy.
   - **Upright choking on a peanut**: Likely found in the **right lower lobe**.
2. **Aspiration Risks**:
   - **Supine**: Right lower lobe (superior segment).
   - **Right lateral**: Right upper lobe.

Diaphragmatic Paralysis (Phrenic Nerve Palsy)

Innervation

- The diaphragm is innervated by the **phrenic nerve (C3, C4, C5)**.

Causes

1. **Unilateral (more common)**:
   - **Trauma**: Thoracic surgery.
   - **Compression**: Cervical spondylosis, cervical tumours.
   - **Infections**: Viral (e.g., herpes zoster, poliomyelitis).
2. **Bilateral**:
   - **Neurological**: Guillain-Barré syndrome.
   - **Infectious**: Severe infections.

Clinical Features

- **Unilateral paralysis**:
  - Usually asymptomatic.
- **Bilateral paralysis**:
  - **Dyspnoea**, which may progress to ventilatory failure.

Diagnosis

1. **Unilateral paralysis**:
   - **Chest X-ray**: Asymmetric elevation of the affected hemidiaphragm.
   - **Spirometry**:
     - Forced vital capacity (FVC) reduced to **70–80%** of predicted in sitting position.
     - Further reduction by **15–25%** in supine position.
   - **Fluoroscopy**:
     - Confirms diagnosis by showing **paradoxical motion** on sniff or forced inspiratory manoeuvres.
2. **Bilateral paralysis**:
   - Fluoroscopy is **inaccurate** for diagnosis.

Treatment

- **Unilateral paralysis:**
  - Typically does **not require treatment**.
- **Bilateral paralysis**:
  - Requires **noninvasive positive pressure ventilation (NPPV)**, such as **bilevel positive airway pressure (BPAP)**.

Lung Physiology

Pulmonary Surfactant

- **Composition**: Phospholipids (e.g., DPPC/lecithin), carbohydrates, proteins.
- **Production:** Released by type 2 pneumocytes, first detectable at 28 weeks of gestation.
- **Function:**
  - Reduces alveolar surface tension, preventing alveolar collapse during expiration.
  - Lowers elastic recoil at low lung volumes, decreasing work of breathing.
  - Maintains lung inflation with minimal pleural pressure (~4 cmH_2O).

Pulmonary Circulation

- **Features:**
  - Low pressure, low flow, and high compliance vessels.
  - Hypoxic vasoconstriction shifts blood to well-ventilated regions, improving gas exchange.
- **Clinical Relevance**:
  - Chronic hypoxia may cause pulmonary hypertension and cor pulmonale.

Chloride Shift

- CO_2 enters RBCs → Carbonic anhydrase converts CO_2 + H_2O to HCO_3^- + H^+.
- H^+ binds haemoglobin; **HCO_3^-** diffuses out, replaced by Cl^-.
- Facilitates CO_2 transport as bicarbonate from peripheral tissues to the lungs.

Oxygen Dissociation Curve

- **Definition**: Relationship between haemoglobin saturation and oxygen partial pressure.
- **Shifts:**
  - **Right Shift**: Increased oxygen delivery (↑H^+, CO_2, 2,3-DPG, temperature).
  - **Left Shift**: Increased oxygen affinity (↓H^+, CO_2, 2,3-DPG, temperature; HbF, CO poisoning).

Causes of shifting the curve to the right or left

Shifts to Right = Raised oxygen delivery (The R rule)	Shifts to Left = Lower oxygen delivery (The L rule)
• Raised [H+] (acidity) • Raised PCO2 • Raised 2,3-DPG • Raised temperature	• Low [H+] (alkali) • Low PCO2 • Low 2,3-DPG • Low temperature • HbF, methemoglobin, carboxyhaemoglobin

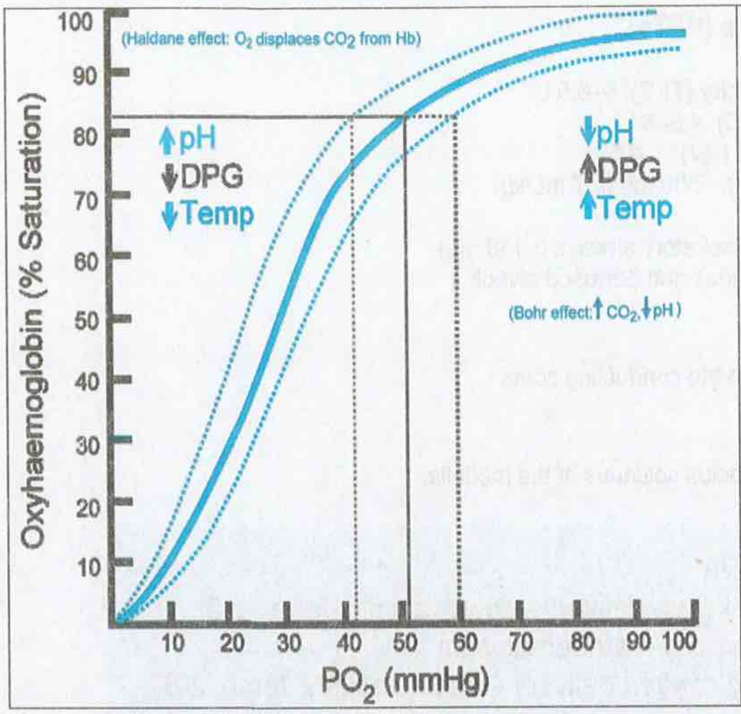


Diagram of Oxygen Dissociation Curve:

- Red line demonstrating shifting to the right.
- The green line demonstrating shifting to the left

Bohr and Haldane Effects

- **Bohr Effect**: High CO_2/H^+ decreases haemoglobin's oxygen affinity, enhancing tissue oxygen delivery (right shift).
- **Haldane Effect**: High O_2 reduces haemoglobin's CO_2 affinity, promoting CO_2 release in the lungs (left shift).

Acclimatisation to High Altitudes

- **Changes**:
  - Erythrocytosis with increased haemoglobin.
  - Increased 2,3-DPG levels.
  - Increased pulmonary artery pressure.
  - Normal respiration and cardiac output with acclimatisation.

Lung Compliance

- **Definition**: Change in lung volume per unit airway pressure.
- **↓ Compliance Causes**: Pulmonary oedema, fibrosis, pneumonectomy, kyphosis.
- **↑ Compliance Causes**: Age, emphysema.

Causes of ↑ compliance	Causes of ↓ compliance
• Age • Emphysema	• Pulmonary edema • Pulmonary fibrosis • Pneumonectomy • Kyphosis

Pulmonary Function Tests (PFTs)

- **Normal Volumes:**
  - **Total Lung Capacity (TLC):** 6–6.5 L.
  - **Vital Capacity (VC):** 4.5–5 L.
  - **Residual Volume (RV):** 1–1.5 L.
  - **Tidal Volume (TV):** ~500 mL or 7 mL/kg.
- **Dead Space:**
  - **Anatomic:** Non-respiratory airways (~150 mL).
  - **Physiologic:** Includes non-perfused alveoli.

Terminal Bronchioles

- Least airway resistance in the conducting zone.

Cough Centre

- Located in the nucleus tractus solitarius of the medulla.

Oxygen dissociation curve

- shifts Left - Lower oxygen delivery - Lower acidity, temp, 2-3 DPG - also HbF, carboxy/methaemoglobin
- shifts Right - Raised oxygen delivery - Raised acidity, temp, 2-3 DPG

Community-acquired pneumonia (CAP)

Definition: Pneumonia acquired outside the hospital or healthcare facility.

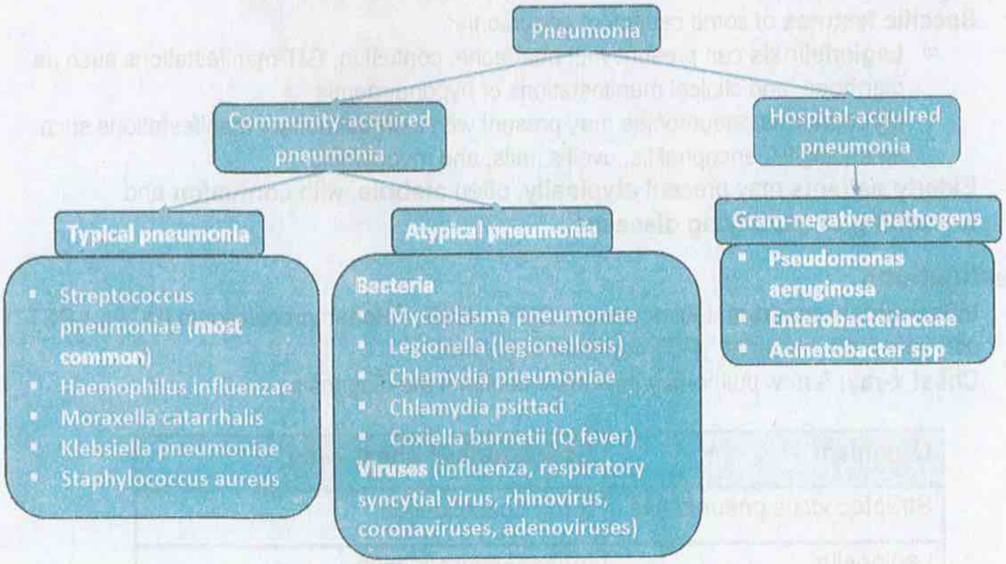
Causes

- ***Streptococcus pneumoniae***
  - ⇨ **the most common cause of CAP & single lobar pneumonia (80%)**
  - ⇨ **commonly causes reactivation of the herpes simplex virus, resulting in 'cold sores' → herpes labialis**
  - ⇨ **the most important cause of fulminant sepsis in patients with hyposplenism.**
- ***Haemophilus influenzae***
  - ⇨ more likely to be associated with exacerbations of **COPD**
- ***Staphylococcus aureus***
  - ⇨ common **after the flu, in the elderly, patients with underlying disease** and intravenous drug users (as often found on the skin. This may be hinted in questions by the presence of track marks)
  - ⇨ causes bibasal pneumonia and can result in cavitating pneumonia. Pneumothorax, pleural effusion and empyema are common.
  - ⇨ **It carries a high mortality rate, and therefore, if suspected, treatment should initially be for a severe CAP.**

- ⇨ Capable of production of Panton-Valentine-Leucocidin toxin, associated with severe illness and high mortality.
- ⇨ the BNF advises the co-prescription of flucloxacillin.

- ***Klebsiella pneumoniae***
  - ⇨ **Classically occurs in alcoholics** (Friedlander's pneumonia) and immunosuppressed individuals
  - ⇨ can cause cavitating pneumonia
  - ⇨ usually affects the upper lobes
  - ⇨ Chest x-ray features may include abscess formation in the middle/upper lobes and empyema.
  - ⇨ The mortality approaches 30-50%.
- **Atypical pneumonia** caused by:
  - ⇨ *Mycoplasma pneumoniae*
  - ⇨ *Legionella pneumophila* .
  - ⇨ Coxiella burnetii (Q fever) → relation to animal sources (usually sheep).
  - ⇨ Chlamydophila psittaci → bird contact (eg, poultry or duck workers)
  - ⇨ *Chlamydophila pneumophila*
- **Viral pneumonia**
  - ⇨ Some studies have found that influenza virus is the most common cause of CAP in adults.

Causes



Types

	Lober pneumonia	Bronchopneumonia	Interstitial Pneumonia
Location	▪ Alveoli ▪ Usually unilateral ▪ Limited by anatomic boundaries	▪ Bronchi ▪ Usually bilateral ▪ Not limited by anatomic boundaries	▪ Interstitium (between alveoli) ▪ Usually bilateral ▪ Not limited by anatomic boundaries
CXR/CT pattern	▪ Dense consolidation ▪ Air bronchogram	Patchy opacities	▪ Diffuse hazy opacities ▪ Ground-glass opacities or reticular patterns ▪ Septal thickening
Causative organism	▪ Streptococcus Pneumoniae ▪ Klebsiella	▪ Mycoplasma ▪ Staph aureus ▪ Chlamydia ▪ Pseudomonas	▪ Viral ▪ PJP ▪ Atypical pathogens (Mycoplasma, Legionella, Chlamydia, Coxiella burnetii)

Features

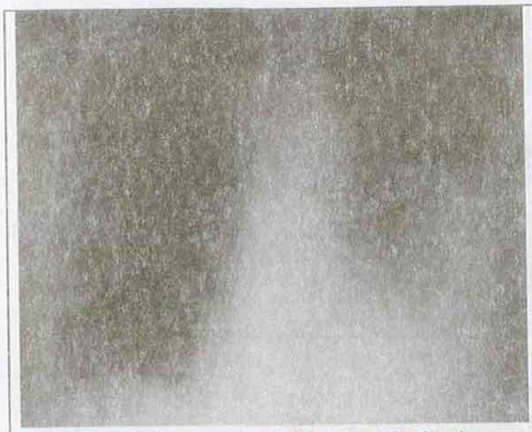
- **Respiratory symptoms** (e.g. cough, often with increasing sputum production, expectoration, dyspnoea, pleuritic pain, and haemoptysis)
- **Signs of infection** (fever or chills and leukocytosis)
- **Specific features** of some causes of pneumonia:
  - ⇨ **Legionellosis** can present with headache, confusion, GIT manifestations such as diarrhoea, and clinical manifestations of hyponatraemia.
  - ⇨ **Mycoplasma** pneumoniae may present with extrapulmonary manifestations such as myringitis, encephalitis, uveitis, iritis, and myocarditis
- **Elderly patients** may present **atypically**, often **afebrile**, with **confusion** and **worsening of underlying diseases.**

Investigations

- **Inflammatory markers:** leukocytosis ↑ CRP, ↑ ESR, ↑ Serum procalcitonin (PCT): ↑ PCT correlates with bacterial, ↓PCT correlated with viral.
- **Chest x-ray:** A new pulmonary infiltration confirms the diagnosis.

Organism	Characteristic chest x-ray
Streptococcus pneumoniae	**lobar** consolidation
Legionella	**bibasal** consolidation
Staphylococcus aureus	bilateral **cavitating** bronchopneumonia,

- **Consider chest CT** or empiric treatment if clinical suspicion for CAP remains high despite a negative CXR, as the initial CXR may be falsely negative.


Left lower lobe opacity with pleural effusion.

Multifocal opacities in bronchopneumonia

Management

- **Assessed the severity of pneumonia using (CURB-65 score)**
  - ⇨ **CURB-65 score criteria**
    1. Confusion (abbreviated mental test score ≤ 8/10)
    2. Urea > 7 mmol/L
    3. Respiratory rate ≥ 30 / min
    4. **BP**: systolic ≤ 90 or diastolic ≤ 60 mmHg
    5. age ≥ 65 years
  - ⇨ CURB-65 score of 0 – 1 can be managed in the community.
  - ⇨ A CURB-65 score of 2 or more should be managed in the hospital as this represents severe community-acquired pneumonia.

- **Empirical antibiotics:** as suggested by the BTS, are shown below.

Pneumonia Severity	1st line	2nd line
Low Severity (CURB65 = 0-1) → Home	Amoxicillin orally	Doxycycline or clarithromycin orally
Moderate severity (CURB65 = 2) → Hospital	Amoxicillin **plus** clarithromycin orally (IV if oral administration not possible)	Doxycycline, Levofloxacin or moxifloxacin orally
High Severity (CURB 65 = 3-5) → Hospital	Co-amoxiclav plus clarithromycin IV	Benzylpenicillin plus levofloxacin or ciprofloxacin IV **OR Cefuroxime plus clarithromycin IV**

- BNF advice: add flucloxacillin if staphylococci are suspected (e.g. In influenza)
- Pneumonia possibly caused by atypical pathogens → Clarithromycin
- If ***Staphylococcus aureus*** is identified, treatment should be altered:

⇨ **Non-MRSA** organisms should be treated with flucloxacillin and/or rifampicin; an alternative for penicillin-allergic patients is teicoplanin and rifampicin.
⇨ **MRSA** should be treated with vancomycin.

Panton-Valentine Leukocidin-producing Staphylococcus aureus (PVL-SA)

- a rare cause of high-severity pneumonia associated with rapid lung cavitation (Necrotising pneumonia) and multiorgan failure.
- empirical antibiotic combination of IV **linezolid** 600 mg twice daily, IV **clindamycin** 1.2 g four times a day and IV rifampicin 600 mg twice daily

Prognostic factors

- **Factors associated with a poor prognosis:**
  - ⇨ ↑ **CURB-65 score** of 4 → mortality rate at 30 days = 30%.
  - ⇨ **Co-morbidity** (renal disease, DM, chronic lung disease, heart failure)
  - ⇨ **Hypoxaemia** (pO2 < 8 kPa) independent of FiO2
  - ⇨ **White cell count** less than 4 ×109/L or greater than 20 ×109/L
  - ⇨ **Multi-lobar involvement on CXR**
  - ⇨ **Temperature less than 35°C or more than 40°C.**
  - ⇨ **Thrombocytosis** is associated with increased mortality compared to thrombocytopenia or normal platelet levels.
- **The risk of mortality increases as the CURB score increases**

Score	Risk of death at 30 days
0 to 1	<5% mortality
2 to 3	**< 10% mortality**
4 to 5	15-30% mortality

- **How quickly their symptoms should resolve?**
  - ⇨ NICE recommend that the following information is given to patients with pneumonia in terms of how quickly their symptoms should resolve:

Time	Progress
1 week	Fever should have resolved
4 weeks	Chest pain and sputum production should have substantially reduced
6 weeks	Cough and breathlessness should have substantially reduced
3 months	Most symptoms should have resolved but fatigue may still be present
6 months	Most people will feel back to normal.

Follow up

- **In patients managed in the community:** review after 48 h, if no improvement → hospital admission + chest radiography + **re-measure C-reactive protein.**
- **A chest X-ray in six weeks to ensure complete resolution and exclude any underlying cause, especially malignancy (radiological changes can take up to six weeks to improve). If persistent shadowing on the lung is present, a respiratory physician should be referred.**

Klebsiella Pneumonia

Pathogen	Gram-negative bacillus encapsulated (part of the normal gut flora)
Risk factor	pneumonia typically following aspiration. **More common in alcoholics** (↓consciousness → Microaspiration)
Type of pneumonia	Common cause of nosocomial pulmonary infections uncommon cause of CAP.
Sputum	'red-currant jelly' sputum
Chest X-ray	**Cavitating lesions**, often affects <u>upper lobes</u>.
Treatment	Non-Extended-spectrum beta-lactamase (ESBL) K→ 3rd generation cephalosporin. ESBL-K pneumoniae → carbapenem

Legionella pneumonia (Legionnaires' disease)

Pathogen	Gram-negative rod, intracellular, aerobic pathogen
Source of infections	Typically **colonises hot water tanks.**
Transmission	▪ **By inhalation of contaminated water droplets (aerosol)** ▪ **Person-to-person transmission is not seen**
Risk factor	Foreign holidays (air-conditioning systems)
Outbreaks	**Can cause outbreaks** in large facilities such as hospitals, hotels, or apartment buildings due to **contaminated communal water supplies**
Typical features	▪ Flu-like symptoms (present in > 95% of patients), dry cough ▪ Gastrointestinal symptoms such as nausea, vomiting, and diarrhea ▪ Elevated hepatic transaminases ▪ **Relative bradycardia** ▪ **Lymphopaenia with** marked **neutrophil leukocytosis** may be associated with concomitant **lymphopenia.** ▪ Hyponatraemia **(Secondary to** syndrome of inappropriate antidiuretic hormone secretion **(SIADH)**
Diagnosis	▪ **Urinary antigen:** the most useful diagnostic test ▪ **Polymerase chain reaction (PCR)** using sputum or bronchoalveolar lavage specimen, **has high diagnostic accuracy** (if available)
Chest X-ray	Diffuse reticular opacities are commonly seen
Treatment	**1st line: Fluoroquinolones (levofloxacin** preferred, ciprofloxacin, moxifloxacin) OR Macrolides (Azithromycin, preferred, clarithromycin) **2nd line:** doxycycline

The **classic features** of Legionnaires' disease are: ⇨ **Recent foreign travel** ⇨ **Relative bradycardia** • **prominent headache** ⇨ **Hyponatraemia**
Legionella pneumophilia is best diagnosed by the urinary antigen test

Mycoplasma pneumoniae

Pathogen	Gram-positive bacteria. It **lacks a cell wall**, so it is not visible on Gram stain and not susceptible to antibiotics that inhibit cell wall synthesis, such as penicillins.
Outbreaks	**It can cause epidemic outbreaks, commonly among people** living in close quarters, such as households, schools, and military facilities.
Typical features	URI and acute bronchitis are the most common (flu-like symptoms classically precede a dry cough)
Extra-pulmonary manifestations (10% of cases)	▪ **Haemolytic anaemia** (50% of cases) due to IgM antibodies (**cold agglutinins**) directed against erythrocyte membrane → **Spherocytes** → **Haemolysis** → **Features of haemolysis (direct Coombs' test,** ↑reticulocyte counts, ↑unconjugated bilirubin, ↑LDH, ↓haptoglobins, **fragmented red blood cells)** ▪ **Hepatitis** ▪ Skin rash: **Erythema multiforme,** erythema nodosum ▪ CNS: Meningoencephalitis, Guillain-Barré syndrome, transverse myelitis ▪ Cardiac: Myocarditis, Pericarditis ▪ Renal failure: acute glomerulonephritis
X-ray	Bilateral interstitial infiltrate (90%). Might not correlate with the patient's condition → much worse than would be suggested by the clinical examination
Mycoplasma serology	▪ **the "gold standard" diagnostic test** ▪ **Positive cold agglutination test** (in 50%)
Treatment	Macrolides (eg, azithromycin), tetracyclines (eg, doxycycline), or respiratory fluoroquinolones (eg, levofloxacin or moxifloxacin).

Aspiration pneumonia

Definition: a type of pneumonia that occurs as a result of oropharyngeal secretions and/or gastric contents aspiration (also known as Mendelson syndrome)

Risk factors

- ↓ level of consciousness (e.g. seizure, Alcohol use, stroke, **post-anaesthesia**) → impaired gag or swallowing reflex → aspiration occurred several weeks earlier.
- Gastroesophageal reflux disease, oesophagal motility disorders, dysphagia.
- poor oral hygiene

Features

- Immediate symptoms: **bronchospasms**, crackles on auscultation, hypoxemia with cyanosis
- Late symptoms: fever, shortness of breath, cough with foul-smelling sputum

Site of aspiration

- **Which lung?:** the **right lung** is commonly affected due to the angle of the bronchi (more vertical and wider than the left main bronchus.)
- **Which lobe?:** depends on patient's position during aspiration:
    - ⇨ **Aspiration while recumbent (lying down): superior segment of the right lower lobe** (most common site of aspiration)
    - ⇨ **Aspiration while sitting upright**: posterior basal segment of the right lower lobe.

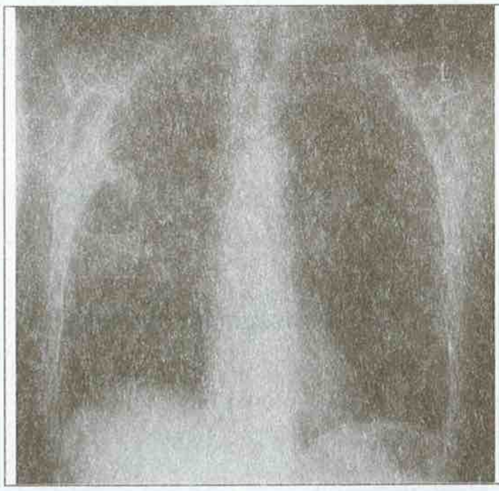
Organisms

- Anaerobes and Gram-negative organisms are the usual organisms in abscesses following aspiration.
- Sputum or tracheal Gram stain reveals mixed flora.

Complications: lung abscess and empyema **(air-fluid level is characteristic of a lung abscess).**

Treatment

	1st choice	Alternative choice
Community-acquired aspiration pneumonia	Amoxicillin-clavulanate or ampicillin-sulbactam (1.5 – 3 g every six hours)	Moxifloxacin
Hospital-acquired aspiration pneumonia	imipenem, meropenem, or piperacillin-tazobactam.	3rd, 4th, or 5th generation cephalosporin PLUS metronidazole (500 mg three times daily). If the patient is allergic to penicillin or cephalosporin → Vancomycin + Metronidazole.



The slide shows an abscess in the right mid-zone.

Psittacosis (Chlamydia psittaci pneumonia) (Atypical pneumonia)

Organism	*Chlamydia psittaci*, an obligate intracellular organism
Transmission	Transmitted to humans from birds (**inhalation of organisms** in dried faeces or in bird feather dust.)
Risk factors	Pet owners, vets and zoo keepers
Typical features	▪ Fever, headache, myalgias, dry cough) **in a patient with a history of bird contact** ▪ Pneumonia, severe headache, splenomegaly, and failure to respond to beta-lactam antibiotics ▪ Abnormal LFTs in up to 50%.
Complications	Respiratory failure, hepatitis, endocarditis, and encephalitis.
Diagnoses	▪ [illegible]: (e.g. microimmunofluorescent antibody testing or complement fixation assay) the most useful diagnostic test ▪ Culture is discouraged since *C. psittaci* is highly infectious when cultured and is only performed in specialized laboratories.
Trématent	▪ **1st line: doxycycline** ▪ **2nd line: macrolides e.g. erythromycin or azithromycin**

Exposure to an ill bird and a rash (Horder's spots) are pathognomonic.

Hospital-acquired pneumonia (HAP), nosocomial pneumonia

Definition: onset > 48 hours after admission

Prevalence: The third most common hospital-acquired infection after urinary tract infections and wound infections.

Causes

- **Gram-negative organisms** are the most common causes, especially aerobic gram-negative bacilli, such as:
  - ⇨ *Pseudomonas aeruginosa*,
  - ⇨ *Escherichia coli*,

- ⇨ *Klebsiella pneumoniae*, and
- ⇨ *Acinetobacter* species.

Diagnosis: chest x-ray or CT scan → new and/or persistent alveolar shadowing.

Treatment: The current British Thoracic Society (BTS) recommendation is to combine a third-generation cephalosporin with an aminoglycoside.

Choice of antibiotic

Antibiotics for adults aged 18 years and over (NICE guidelines, September 2019)	
Treatment	**Antibiotic**
First-choice oral antibiotic **if non-severe** symptoms or signs and not at higher risk of resistance (guided by microbiological results when available)	Co-amoxiclav
Alternative oral antibiotics if **non-severe symptoms or signs, and not at higher risk of resistance, for penicillin allergy or if co-amoxiclav** unsuitable.	Doxycycline Cefalexin (caution in penicillin allergy) Levofloxacin
First-choice if severe symptoms or signs (e.g. sepsis) or ↑ risk of resistance.	Piperacillin with tazobactam Ceftazidime Ceftriaxone Cefuroxime Meropenem Ceftazidime with avibactam Levofloxacin
If suspected or confirmed methicillin-resistant *Staphylococcus aureus* infection (dual therapy with a first-choice intravenous antibiotic)	Vancomycin Teicoplanin Linezolid (if vancomycin cannot be used)

Pseudomonas pneumonia

<table>
<tr><td>Organism</td><td>Pseudomonas aeruginosa is a Gram-negative, rod-shaped bacterium</td></tr>
<tr><td>Transmission</td><td>Primarily transmitted in healthcare settings but can also spread in the community under certain conditions.</td></tr>
<tr><td>Risk factors</td><td>• P. aeruginosa is a common cause of gram-negative hospital-acquired pneumonia
• Community-acquired P. aeruginosa pneumonia occurs mainly in:
⇨ immunocompromised patients (eg, HIV, post-transplant, or neutropenic hosts)
⇨ structural lung abnormalities (e.g. cystic fibrosis, bronchiectasis, COPD)
• Nosocomial or hospital-acquired infections should be suspected in patients with an onset of symptoms at least 48 hours after admission to the hospital.</td></tr>
<tr><td>Complications</td><td>Respiratory failure, Septicemia</td></tr>
<tr><td>Diagnoses</td><td>Sputum culture, blood culture</td></tr>
<tr><td>Trématent</td><td>
<table>
<tr><th>Class</th><th>Agent</th></tr>
<tr><td>Penicillin-beta-lactamase combinations</td><td>Piperacillin-tazobactam (the only antipseudomonal penicillin)</td></tr>
<tr><td>Cephalosporins</td><td>Ceftazidime or Cefepime</td></tr>
<tr><td>Fluoroquinolones</td><td>Ciprofloxacin or Levofloxacin (the only oral antibiotics with antipseudomonal activity)</td></tr>
<tr><td>Carbapenems</td><td>Meropenem, Imipenem</td></tr>
</table>
</td></tr>
</table>

Pneumocystis Jirovecii pneumonia (PCP)

Aspect	Details
Definition	Opportunistic fungal infection caused by *Pneumocystis jirovecii*, affecting immunocompromised individuals.
Risk Factors	HIV/AIDS (CD4 count <200 cells/μL), organ transplant, prolonged corticosteroid use, immunosuppressive therapy.
Clinical Features	Progressive dyspnea, non-productive cough, fever, hypoxia, possible chest tightness.
Diagnosis	- **Imaging**: Chest X-ray shows bilateral interstitial infiltrates; CT shows ground-glass opacities. - **Lab tests**: Induced sputum or bronchoalveolar lavage (BAL) for PCR or staining (e.g., silver stain).
Management	- **First-line treatment**: Oral or IV trimethoprim-sulfamethoxazole (TMP-SMX) 15–20 mg/kg/day in divided doses for 21 days. - **Adjunctive therapy**: Corticosteroids if PaO2 <70 mmHg or A-a gradient >35 mmHg (e.g., prednisone 40 mg twice daily for 5 days, taper over 21 days).
Prophylaxis	TMP-SMX 1 double-strength tablet daily or three times weekly for high-risk patients (e.g., CD4 count <200 cells/μL).
Complications	Respiratory failure, pneumothorax, long-term lung damage in severe cases.

Obstructive vs. Restrictive lung diseases

Obstructive vs Restrictive Lung Diseases Comparison

Aspect	Obstructive Lung Diseases	Restrictive Lung Diseases
Definition	Airflow limitation due to obstruction in the airways	Reduced lung expansion, leading to decreased lung volumes
Mechanism	Difficulty exhaling air due to trapped air in the lungs	Difficulty inhaling air due to restricted lung expansion
Common Causes	COPD, asthma, bronchitis, emphysema	Pulmonary fibrosis (↑↑**High elastic recoil**), sarcoidosis, obesity, scoliosis, neuromuscular diseases, respiratory muscle weakness.
Lung Volumes	Increased TLC and RV	Decreased TLC, FRC, and RV
Spirometry Pattern	Reduced FEV1 (<80%) Normal or reduced FVC Decreased FEV1/FVC ratio (<70%)	Reduced FEV1 (<80%) Reduced FVC (<70%) Normal or increased FEV1/FVC ratio (> 70%)
Key Difficulty	Difficulty exhaling air	Difficulty inhaling air

Physiological lung volumes

Lung volume	Definition	Normal range
Total lung capacity (TC, TLC)	• Volume of air in the lungs after maximal inhalation • TC = VC + RV	6–6.5 L
Vital capacity (VC)	• Difference in lung volume between maximal exhalation and maximal inhalation • VC = TV + IRV + ERV	4.5–5 L
Residual volume (RV)	• Volume of air that remains in the lungs after a maximal exhalation	1–1.5 L
Tidal volume (TV)	• Volume of air that is inhaled and exhaled in a normal breath at rest	~ 500 mL or 7 mL/kg
Inspiratory reserve volume (IRV)	• Maximum volume of air that can still be forcibly inhaled following the inhalation of a normal TV	3–3.5 L
Inspiratory capacity (IC)	• Maximum volume of air that can be inhaled after the exhalation of a normal TV • IRC = IRV + TV	3.5–4 L
Expiratory reserve volume (ERV)	• Maximum volume of air that can still be forcibly exhaled after the exhalation of a normal TV	1.5 L
Expiratory capacity (EC)	• Maximum volume of air that can be exhaled after the inspiration of a normal TV • ERC = ERV + TV	2 L

Lung volume	Definition	Normal range
Functional residual capacity (FRC)	• Volume of air that remains in the lungs after the exhalation of a normal TV • FRC = RV + ERV	2.5–3 L

Spirometry:

- **Purpose:** Measures lung function, specifically the amount (volume) and speed (flow) of air that can be inhaled and exhaled. It helps diagnose obstructive and restrictive lung diseases.
- **Key Parameters:**
  - ⇨ Forced Vital Capacity (FVC): Total volume of air that can be exhaled forcefully after full inspiration.
  - ⇨ Forced Expiratory Volume in 1 Second (FEV1): Volume of air exhaled in the first second during the FVC manoeuvre.
  - ⇨ FEV1/FVC ratio: A key indicator in differentiating obstructive from restrictive lung disease.
- **Interpretation:**
  - ⇨ Obstructive lung disease (e.g., COPD, asthma): FEV1 is reduced, FVC may be normal or reduced, FEV1/FVC < 70%.
  - ⇨ Restrictive lung disease (e.g., pulmonary fibrosis): Both FEV1 and FVC are reduced, but FEV1/FVC ratio remains normal or high (>70%).

Peak expiratory flow rate (PEFR)

- **Definition:** The maximum airflow rate attained during forced expiration.
- **Normal values**
  - ⇨ PEF values are usually expressed as L/min; when measured as part of spirometry, values are expressed in L/sec. To convert, multiply L/sec x 60 sec/min = L/min.
  - ⇨ Peak flow meters are handheld devices used to measure PEFR in the ambulatory setting
  - ⇨ Normally : ≥ 80% of the predicted average value
  - ⇨ It depends upon factors such as gender, age, and height. **The most accurate correlation of PEFR is with height.** PEFR is typically higher in males than females and higher in taller patients.
- **Advantages**
  - ⇨ It is effort-independent.
  - ⇨ In patients with asthma, the PEFR % predicted correlates reasonably well with the FEV_1 and provides an objective measure of airflow limitation when spirometry is not available
- **Disadvantages**
  - ⇨ predominantly assesses large airway calibre and can underestimate the effects of asthma in small airways.
  - ⇨ Restrictive processes that limit full inspiration, such as chest wall disease, obesity, and muscle weakness, can reduce PEF without airflow limitation. Thus, values for PEF that are less than 80% of what is predicted should be further evaluated with spirometry before assuming that the abnormality is due to asthma.

- **The differences between Peak Flow Meters and Spirometry**

Peak Flow Meter	Spirometry
⇨ Measures ability to exhale ⇨ Will vary with lung capacity ⇨ Used with charts to detect **OBSTRUCTIVE** disease ⇨ It can be used by patients to monitor lung 'function'	⇨ Simultaneous measurement of flow and capacity ⇨ It can be used to diagnose both **OBSTRUCTIVE** and **RESTRICTIVE** disease (gold standard) ⇨ Costs more than peak flow meters

Flow-volume loop

- provides additional information about the location of airway constriction
- **Best test for upper-way obstruction.** The upper airway is defined as that portion of the airway extending from the mouth to the mainstem bronchi

Explanation of high FEV-1/FVC ratio in lung fibrosis
- Lung fibrosis → ↑↑**high elastic recoil** → most forced expiratory volume (FEV-1) will be expelled in the first second compared to full forced expiration → a relatively high FEV-1/FVC ratio.

Obesity → extra-thoracic restriction
- **Obesity could show a significant restrictive defect.**

Patients with respiratory muscle weakness show spirometric findings of restrictive lung disease.

- **What is the best pre-operative screen of pulmonary function for a smoker patient evaluated for a coronary artery bypass graft (CABG).?**
  ⇨ **Ratio of the forced expiratory volume in 1 second to the forced vital capacity**

Flow volume loop is the investigation of choice for upper airway compression

Transfer Factor (DLCO/TLCO)

Definition

- **DLCO/TLCO**: Measure of the lung's ability to transfer gas from the alveoli to the blood by assessing the uptake of carbon monoxide (CO), which mimics oxygen transfer.

Components Affecting DLCO

1. **Alveolar-capillary membrane integrity**:
   - Thickness and surface area.
2. **Haemoglobin concentration**:
   - CO binds to haemoglobin in red blood cells.
3. **Pulmonary blood flow**:
   - Adequate capillary perfusion is essential.

Clinical Interpretation

- **Increased DLCO**:
  - Pulmonary haemorrhage (e.g., Goodpasture's syndrome).
  - Polycythaemia.
  - Left-to-right cardiac shunts.
  - Asthma (sometimes due to increased blood flow).
- **Decreased DLCO**:
  - **Obstructive Diseases**:
    - Emphysema (due to alveolar destruction).
  - **Restrictive Diseases**:
    - Pulmonary fibrosis (thickened alveolar membrane).
    - Sarcoidosis.
    - Asbestosis.
  - **Vascular Diseases**:
    - Pulmonary hypertension.
    - Chronic thromboembolic disease.
  - **Other**:
    - Anaemia (reduced haemoglobin for CO uptake).

Causes of a raised DLCO	Causes of a lower DLCO
• Asthma • Pulmonary haemorrhage (Wegener's, Goodpasture's) • Left-to-right cardiac shunts • Polycythaemia • Hyperkinetic states • Early left heart failure • Male gender • Exercise • Obesity	• Pulmonary fibrosis • Pneumonia • Pulmonary emboli • Pulmonary oedema • Emphysema • bronchiolitis obliterans • Anaemia • Low cardiac output • Pulmonary AV malformations • carboxyhemoglobinemia. • hepatopulmonary syndrome • lymphangioleiomyomatosis

Transfer factor
- raised: asthma, haemorrhage, left-to-right shunts, polycythaemia
- low: everything else

Clinical Utility
- **Obstructive vs Restrictive Disease**:
  - DLCO can differentiate emphysema (low DLCO) from asthma (normal or high DLCO).
- **Interstitial Lung Disease**:
  - Lowered DLCO correlates with severity.
- **Pulmonary Vascular Disease**:
  - Low DLCO indicates vascular involvement (e.g., pulmonary hypertension).
- **Anaemia/Polycythaemia**:
  - DLCO results must be corrected for haemoglobin levels.

Measurement Procedure
- Patient inhales a small amount of CO and holds their breath.
- Exhaled gas is analysed to determine CO uptake.

Limitations
- Dependent on patient effort during the test.
- Requires adjustment for haemoglobin levels, lung volume, and other factors.

Key Points for MRCP
- **High DLCO**: Think pulmonary haemorrhage or increased blood volume.
- **Low DLCO**: Common in emphysema, pulmonary fibrosis, and pulmonary vascular diseases.
- Differentiates obstructive diseases (asthma vs emphysema) and assesses severity in interstitial lung disease.

Transfer Coefficient of Carbon Monoxide (KCO)
Definition
- **KCO**: The transfer factor of carbon monoxide (DLCO) corrected for alveolar volume, reflecting gas exchange efficiency per unit of lung volume.

Clinical Interpretation
1. ↑ KCO:
   - **Causes**:
     - **Post-pneumonectomy**: Compensatory increase in remaining lung units.
     - **Pulmonary haemorrhage**: Increased haemoglobin available for CO uptake.
     - **Polycythaemia**: Increased red blood cells enhancing gas exchange.
     - **Asthma**: Temporary increase due to hyperinflated alveoli.
   - **Clinical Implications**: Reflects improved CO uptake efficiency in certain conditions.

2. ↓ **KCO**:
    - **Causes**:
        - **Emphysema**: Alveolar destruction reduces gas exchange efficiency.
        - **Interstitial Lung Disease**: Thickened alveolar-capillary membrane.
        - **Pulmonary Vascular Diseases**: Reduced perfusion limits gas exchange (e.g., pulmonary hypertension, embolism).
        - **Anaemia**: Reduced haemoglobin decreases CO binding.
    - **Clinical Implications**: Indicates impaired gas exchange at the alveolar-capillary interface.

Utility

- Helps differentiate causes of decreased DLCO:
    - **Low DLCO with low KCO**: Likely due to intrinsic lung disease or vascular abnormalities.
    - **Low DLCO with normal or high KCO**: Suggests extrapulmonary causes (e.g., post-pneumonectomy).

Key Points for MRCP

- **KCO** normalises DLCO for alveolar volume and is particularly useful in conditions with altered lung volumes.
- ↑ **KCO**: Seen in conditions with preserved alveoli but increased efficiency (e.g., pulmonary haemorrhage, polycythaemia).
- ↓ **KCO**: Associated with conditions impairing alveolar or vascular function (e.g., emphysema, interstitial lung disease, anaemia).

Comparison: KCO vs DLCO

Feature	DLCO (Diffusing Capacity of the Lung for CO)	KCO (Transfer Coefficient of CO)
Definition	Total capacity of the lungs to transfer carbon monoxide (CO).	DLCO corrected for alveolar volume, reflecting gas exchange efficiency per unit of lung volume.
Measurement	Absolute value of CO uptake.	Ratio of DLCO to alveolar volume (DLCO/VA).
Units	mL/min/mmHg	mL/min/mmHg/L
Affected by Lung Volume	Decreases proportionally with reduced alveolar volume.	Independent of lung volume; measures efficiency per unit volume.
Clinical Relevance	- Assesses overall gas exchange function.	- Indicates efficiency of gas exchange relative to lung volume.
↑ Values	- Pulmonary haemorrhage, polycythaemia, asthma, left-to-right cardiac shunts.	- Post-pneumonectomy, pulmonary haemorrhage, polycythaemia, asthma.
↓ Values	- Emphysema, interstitial lung disease, pulmonary vascular diseases, anaemia.	- Emphysema, interstitial lung disease, pulmonary vascular diseases, anaemia.
Utility	- Detects lung diseases causing impaired gas exchange.	- Differentiates causes of low DLCO: lung destruction vs. low lung volumes.
Example Applications	- Overall lung capacity to transfer CO.	- Efficiency of remaining functional lung (e.g., post-pneumonectomy).

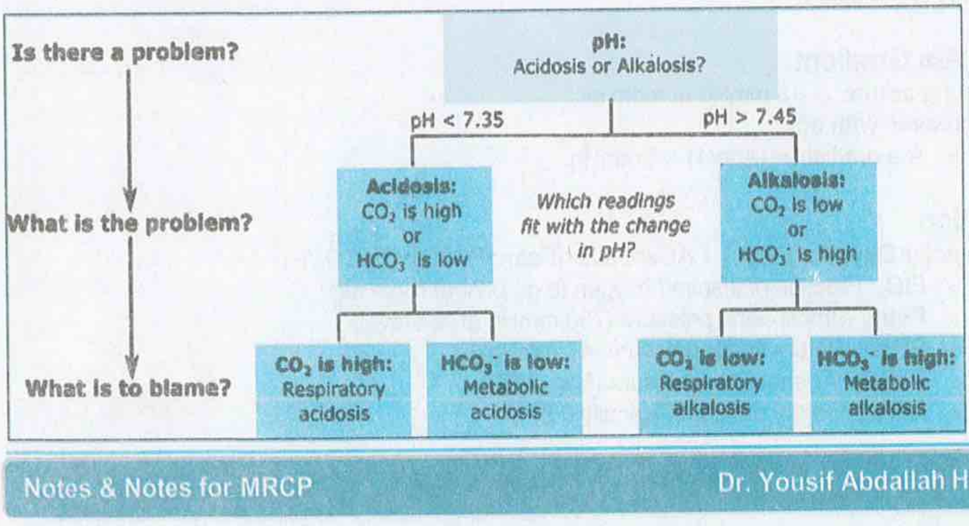
Key Points

- DLCO: Total gas exchange capacity of the lungs; reduced in diseases affecting alveolar-capillary function or blood flow.
- KCO: Normalises DLCO for alveolar volume; helpful in conditions like post-pneumonectomy or low lung volumes to assess efficiency per unit volume.

Arterial Blood Gas (ABG)

Step-by-Step Approach to ABG Interpretation

1. **Check pH**:
   - **Normal**: 7.35–7.45.
   - **Acidosis**: pH < 7.35.
   - **Alkalosis**: pH > 7.45.
2. **Assess PaCO2**:
   - **Normal**: 35–45 mmHg.
   - **Respiratory Acidosis**: PaCO2 > 45 mmHg.
   - **Respiratory Alkalosis**: PaCO2 < 35 mmHg.
3. **Evaluate HCO3- (Bicarbonate)**:
   - **Normal**: 22–26 mEq/L.
   - **Metabolic Acidosis**: HCO3- < 22 mEq/L.
   - **Metabolic Alkalosis**: HCO3- > 26 mEq/L.
4. **Determine Primary Disorder**:
   - Match pH with PaCO2 or HCO3- to identify primary disorder (e.g., low pH with high PaCO2 indicates primary respiratory acidosis).
5. **Compensation Check**:
   - Evaluate if compensation is appropriate (e.g., in metabolic acidosis, PaCO2 should decrease to partially compensate).
6. **Anion Gap Calculation** (for metabolic acidosis):
   - **Equation**: AG = Na+ - (Cl- + HCO3-).
   - **Normal AG**: 8–12 mEq/L.
   - **High Anion Gap Acidosis**: Suggests accumulation of unmeasured acids (e.g., lactic acidosis).
   - **Normal Anion Gap Acidosis**: Suggests loss of bicarbonate or hyperchloremic acidosis.



- Hypoxemic respiratory failure (type 1 respiratory failure): ↓ $PaO2$
- Hypercapnic respiratory failure (type 2 respiratory failure): ↑ $PaCO2$ and ↓ $PaO2$
- **Mixed metabolic and respiratory acidosis**
  - ⇨ pH → below 7.35
  - ⇨ PCO_2 → elevated (> 6 kP_a) indicating a respiratory cause for acidosis
  - ⇨ Bicarbonate → reduced (< 20 mmol/L), contributing to the acidosis.
  - ⇨ **the most likely biochemical imbalance seen in fluid inhalation is → Mixed metabolic and respiratory acidosis**
    - inhalation of fluid → disordered gas exchange → respiratory acidosis.
    - Metabolic acid results from intravascular volume depletion, hypotension and consequent tissue hypoxia.
- **Compensated respiratory acidosis → normal PH, high CO_2, low O_2**
  - ⇨ The fact that the pH is normal means that there must be bicarbonate retention to compensate.
  - ⇨ In **bronchopulmonary dysplasia**, there is usually long-term CO_2 retention with a compensatory increase in bicarbonate leading to a positive base excess and normal pH.
- Pathophysiological changes in case of acute acidosis:
  - ⇨ Occurred too quickly for metabolic compensation to occur via renal bicarbonate reabsorption, which takes 3-5 days to occur. **(bicarbonate will be normal in acute respiratory acidosis)**
  - ⇨ The oxygen dissociation curve is shifted to the right in acute acidosis, i.e. haemoglobin has a decreased affinity for oxygen.
  - ⇨ High pulmonary pressures would be expected after arrest scenario, as the **pulmonary arterioles constrict in response to hypoxia.**

Alveolar-Arterial (A-a) Oxygen Gradient

Definition

- The **A-a oxygen gradient** measures the difference between the oxygen concentration in the alveoli (A) and arterial blood (a), reflecting the efficiency of oxygen transfer from the lungs to the blood.

Normal A-a Gradient

- **Young adults**: 5–15 mmHg at room air.
- **Increases with age**:
  - A-a gradient ≈ (Age/4) + 4 mmHg.

Calculation

1. **Alveolar Oxygen (PAO_2)**: $PAO2=FIO2\times(Patm-PH2O)-(PaCO_2/R)$
   - **FIO_2**: Fraction of inspired oxygen (e.g., 0.21 at room air).
   - **Patm**: Atmospheric pressure (760 mmHg at sea level).
   - **PH_2O**: Water vapour pressure (47 mmHg).
   - **$PaCO_2$**: Arterial CO_2 pressure (from ABG).
   - **R**: Respiratory quotient (typically 0.8).

2. **A-a Gradient**: A−a =PAO2−PaO2
   - **PaO_2**: Arterial oxygen (from ABG).

Clinical Significance

- **Normal A-a gradient**:
  - Hypoxia caused by hypoventilation or low inspired oxygen (e.g., high altitude).
- **Elevated A-a gradient**:
  - Indicates impaired gas exchange, due to:
    - **V/Q mismatch**: Pulmonary embolism, pneumonia.
    - **Shunt**: Atelectasis, ARDS.
    - **Diffusion impairment**: Pulmonary fibrosis, interstitial lung disease.

Causes of Increased A-a Gradient

Category	Examples
Ventilation-Perfusion (V/Q) Mismatch	COPD, asthma, pulmonary embolism, pneumonia.
Shunt	Cardiac shunts, ARDS, atelectasis.
Diffusion Defects	Pulmonary fibrosis, interstitial lung disease, pulmonary oedema.
Others	Ageing, high inspired oxygen (FiO_2), anaemia, or reduced cardiac output.

Causes of Hypoxaemia with Normal A-a Gradient

Cause	Mechanism	Examples
Hypoventilation	Reduced alveolar ventilation decreases oxygen delivery to the lungs.	- Central respiratory depression (e.g., opioids, sedatives, brainstem injury). - Neuromuscular disorders (e.g., Guillain-Barré, myasthenia gravis). - Chest wall disorders (e.g., kyphoscoliosis, obesity hypoventilation syndrome).
Low Inspired Oxygen	Reduced oxygen content in inspired air.	- High-altitude environments (low barometric pressure). - Breathing low-oxygen gas mixtures.

Key Points for MRCP

1. A **normal A-a gradient** rules out significant V/Q mismatch, shunting, or diffusion impairment.
2. Hypoxia with **elevated A-a gradient** points to lung pathology or gas exchange inefficiency.
3. Calculate A-a gradient in patients with hypoxia to narrow differential diagnoses.

An increased A-a gradient may occur in hypoxemia due to shunting, ventilation-perfusion mismatch, or impaired gas diffusion across the alveoli due to fibrosis or edema.

The A-a gradient remains normal with hypoventilation due to CNS and neuromuscular disorders (no diffusion defect) and in high altitude (despite a lower fraction of inhaled O2).

Chest X-ray Findings and Interpretations

Normal Chest X-ray

- **Trachea**: Central or slightly right-shifted.
- **Lung fields**: Equal radiolucency bilaterally.
- **Heart size**: <50% of the thoracic width on PA view.
- **Diaphragm**: Right hemidiaphragm higher than left, sharp costophrenic angles.
- **Mediastinum**: Symmetrical; normal contours.
- **Bones**: Normal alignment and density.

Common Abnormal Findings

Finding	Description	Examples of Causes
Increased Opacity	Localised or diffuse white areas in lung fields.	Pneumonia, pulmonary oedema, atelectasis, ARDS, lung tumour.
Hyperlucency	Increased radiolucency of lung fields.	Emphysema, pneumothorax, air trapping (e.g., asthma).
Pleural Effusion	Blunted costophrenic angles, meniscus sign.	Congestive heart failure, infections (empyema), malignancy, trauma.
Pneumothorax	Absence of lung markings, visible pleural line.	Trauma, spontaneous rupture of bullae, mechanical ventilation.
Consolidation	Homogeneous opacity with air bronchograms.	Lobar pneumonia, pulmonary haemorrhage, aspiration.
Atelectasis	Loss of lung volume, mediastinal shift towards opacity.	Mucus plugging, post-surgical collapse, bronchial obstruction.
Interstitial Pattern	Fine or coarse reticular or nodular opacities.	Pulmonary fibrosis, sarcoidosis, interstitial lung diseases (ILD).
Cardiomegaly	Heart width >50% of thoracic width on PA film.	Congestive heart failure, pericardial effusion, valvular heart disease.
Mediastinal Widening	Enlarged mediastinum.	Aortic dissection, lymphadenopathy, mediastinal tumours.
Kerley B Lines	Horizontal lines at lung bases.	Pulmonary oedema (secondary to left heart failure).
Air Under Diaphragm	Free air beneath the diaphragm on erect CXR.	Perforated viscus (e.g., peptic ulcer).
Hilar Enlargement	Enlarged or abnormal hilar contours.	Sarcoidosis, lymphoma, tuberculosis, metastatic cancer.

Specific Patterns

Pattern	Description	Examples
Batwing/Butterfly	Perihilar consolidation with sparing of lung peripheries.	Pulmonary oedema (secondary to heart failure).
Honeycombing	Thick-walled cystic spaces, usually subpleural.	End-stage pulmonary fibrosis, idiopathic interstitial pneumonia.

Pattern	Description	Examples
Ground-glass Opacity	Hazy lung field with preserved bronchial markings.	Interstitial pneumonia, ARDS, hypersensitivity pneumonitis, early pulmonary oedema.
Cavitation	Circular area with air-fluid level or lucent centre.	Tuberculosis, abscess, fungal infections (e.g., aspergillosis), malignancy.

Differential Diagnosis of Diffuse Opacities on Chest X-ray:

Category	Examples	Key Features
Infectious Causes	- Viral pneumonia (e.g., influenza, COVID-19).	Diffuse opacities, often bilateral; associated fever and respiratory symptoms.
	- Atypical bacterial pneumonia (e.g., Mycoplasma, Legionella).	Patchy or diffuse infiltrates.
	- Fungal pneumonia (e.g., Pneumocystis jirovecii).	Ground-glass opacities, especially in immunocompromised patients.
	- Miliary tuberculosis.	Diffuse fine nodular opacities due to haematogenous spread.
Cardiogenic Causes	- Cardiogenic pulmonary oedema.	Batwing or butterfly distribution, Kerley B lines, pleural effusion.
	- Non-cardiogenic pulmonary oedema (e.g., ARDS).	Bilateral diffuse opacities without cardiomegaly.
Interstitial Lung Diseases (ILDs)	- Idiopathic pulmonary fibrosis, sarcoidosis.	Reticular, nodular opacities; honeycombing in advanced fibrosis.
	- Hypersensitivity pneumonitis, organising pneumonia.	Diffuse or patchy opacities; associated with environmental or occupational exposures.
	- Connective tissue disease-associated ILD (e.g., scleroderma, RA).	Diffuse reticular opacities, often with systemic symptoms.
Vascular Causes	- Pulmonary haemorrhage (e.g., Goodpasture's, vasculitis).	Diffuse alveolar opacities, haemoptysis, and anaemia.
	- Pulmonary embolism (rarely diffuse).	Localised or peripheral wedge-shaped infarcts, rarely diffuse.
Neoplastic Causes	- Lymphangitis carcinomatosis.	Diffuse interstitial pattern due to metastatic tumour spread in lymphatics.
Occupational/Environmental	- Pneumoconioses (e.g., asbestosis, silicosis, coal workers' pneumoconiosis).	Diffuse reticular or nodular opacities; zone-specific (upper zones for silicosis, lower zones for asbestosis).

Category	Examples	Key Features
Drug-Induced Lung Disease	- Amiodarone, methotrexate, bleomycin.	Diffuse interstitial or alveolar opacities depending on the drug.
Systemic Causes	- Autoimmune diseases (e.g., lupus, vasculitis).	Diffuse infiltrates with systemic symptoms (e.g., rash, joint pain).
	- Acute respiratory distress syndrome (ARDS).	Bilateral diffuse opacities due to alveolar damage, non-cardiogenic pulmonary oedema.
Miscellaneous	- Pulmonary alveolar proteinosis.	Diffuse ground-glass opacities with "crazy-paving" on CT.
	- Eosinophilic pneumonia.	Peripheral or diffuse opacities with eosinophilia.

Coin Lesions (Solitary Pulmonary Nodule)

Cause	Examples
Malignant Tumours	Lung cancer, metastases.
Benign Tumours	Hamartoma.
Infections	Pneumonia, abscess, tuberculosis, hydatid cyst.
Vascular	Arteriovenous malformations (AVMs).

White Lung Lesions (White-Outs)

Causes	Tracheal Position	Examples
Pulled Toward White-Out	Trachea deviated toward opacification.	Pneumonectomy, complete lung collapse (atelectasis), pulmonary hypoplasia.
Central	Trachea remains central.	Consolidation, pulmonary oedema (bilateral), mesothelioma.
Pushed Away from White-Out	Trachea deviated away from opacification.	Pleural effusion, diaphragmatic hernia, large thoracic mass.

Characteristics of Consolidation

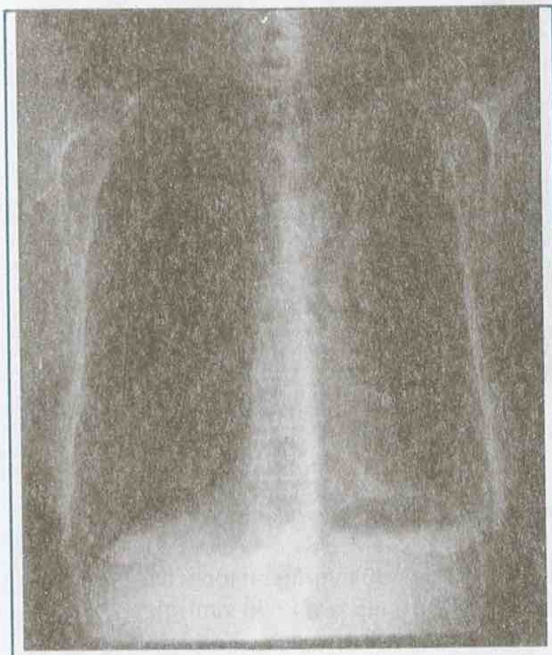
Lobe Involved	Key X-Ray Signs
Left Lower Lobe	Loss of diaphragm clarity.
Left Lingula	Loss of left heart border.
Right Middle Lobe	Obscures right heart border (right atrial edge); superior extent demarcated by the horizontal fissure.
Right Upper Lobe	Upward displacement of the horizontal fissure; enlarged right hilum; opacity abutting the horizontal fissure.

Lobar Collapse (Atelectasis)

Key Signs	Examples
X-Ray Signs	- Tracheal and mediastinal shift toward collapse.
	- Elevated hemidiaphragm.
	- Loss of lung volume on the affected side.
Causes	- Lung cancer (most common in older adults).
	- Foreign body.
	- Mucous plugging (e.g., cystic fibrosis, asthma, post-op complications).

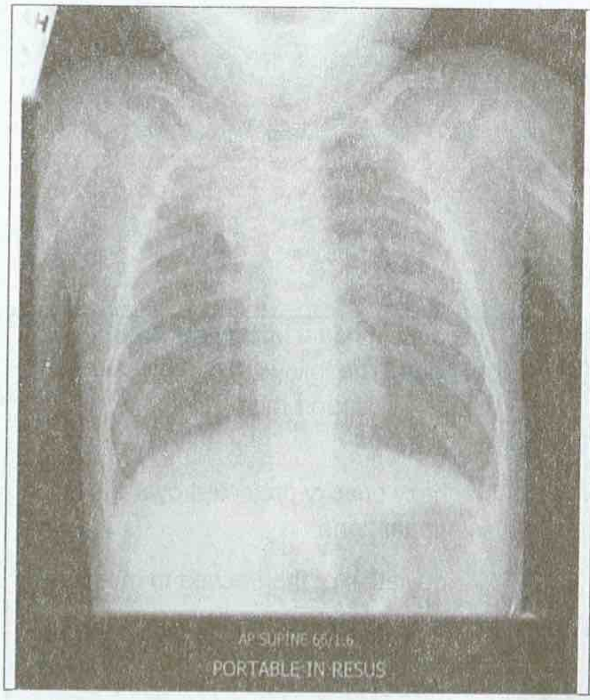
Examples

- **Left Upper Lobe Collapse**:
  - Hazy opacity over the left upper zone.
  - Tracheal deviation to the left.
  - Elevated left hemidiaphragm.
  - Loss of lung volume on the left side.
- **Right Upper Lobe Collapse**:
  - Increased opacity in the right upper zone.
  - Horizontal fissure displaced upward.



This patient has a **left upper lobe collapse**. The following can be seen on the film to support this:

- hazy opacity projected over the left upper zone
- deviation of the trachea to the left
- elevation of the left hemidiaphragm
- loss of lung volume in the left hemithorax



Lung collapse (**Atelectasis**)

- There is increased opacity in the right upper zone, The lateral / inferior border of the shadowing actually represents the horizontal fissure which has been 'dragged' upwards.

Respiratory Failure

Definition

Respiratory failure occurs when the respiratory system fails to maintain adequate gas exchange, leading to:

- **Hypoxaemia**: Arterial oxygen tension (PaO_2) < 8 kPa (< 60 mmHg) on room air.
- **Hypercapnia**: Arterial carbon dioxide tension ($PaCO_2$) > 6.5 kPa (> 50 mmHg).

Types of Respiratory Failure

Type	Definition	Causes
Type 1 (Hypoxaemic)	PaO_2 < 8 kPa with normal or low $PaCO_2$.	- Pneumonia - Pulmonary oedema - Pulmonary embolism - ARDS - Fibrosis
Type 2 (Hypercapnic)	PaO_2 < 8 kPa with $PaCO_2$ > 6.5 kPa.	- COPD - Asthma - Neuromuscular disorders - Obesity hypoventilation - Chest wall disorders
Type 3 (Perioperative)	Respiratory failure due to atelectasis post-surgery.	- Post-anaesthesia - Reduced ventilation due to pain or sedation.
Type 4 (Shock-related)	Respiratory failure due to impaired oxygen delivery from circulatory failure.	- Septic shock - Cardiogenic shock.

Key Points for MRCP

- **Type 1**: Associated with V/Q mismatch or diffusion issues; $PaCO_2$ remains normal due to compensatory hyperventilation.
- **Type 2**: Indicates ventilatory failure; always check for neuromuscular causes and hypercapnic drive.
- **Type 3**: Common after surgery; early mobilisation and respiratory physiotherapy are critical.
- **Type 4**: Requires managing underlying circulatory failure.

Comparison: Obstructive vs Restrictive Lung Disease

Feature	Obstructive Lung Disease	Restrictive Lung Disease
Definition	Airway obstruction leading to difficulty in exhaling air.	Reduced lung compliance or lung volume affecting inhalation.
Examples	- COPD (emphysema, chronic bronchitis) - Asthma - Bronchiectasis - Cystic fibrosis	- Pulmonary fibrosis - Sarcoidosis - Pneumoconiosis - Obesity - Neuromuscular disorders
Spirometry	- FEV1/FVC < 70% - FEV1 significantly reduced - Normal or increased total lung capacity (TLC)	- FEV1/FVC normal or increased - Proportionally reduced FEV1 and FVC - Reduced TLC, functional residual capacity (FRC), and residual volume (RV)
Lung Volumes	- Increased residual volume (RV) and total lung capacity (TLC) due to air trapping.	- Decreased lung volumes (TLC, RV, FRC) due to restricted lung expansion.
Gas Exchange	- V/Q mismatch in advanced disease (e.g., emphysema). - DLCO decreased in emphysema, normal in asthma.	- DLCO reduced in interstitial lung diseases.
Chest X-Ray Findings	- Hyperinflated lungs - Flattened diaphragm - Increased retrosternal airspace (in COPD).	- Reduced lung volumes - Reticular or nodular opacities in interstitial lung disease.
Treatment Approach	- Bronchodilators (e.g., β2-agonists, anticholinergics) - Anti-inflammatory agents (e.g., corticosteroids) - Smoking cessation.	- Treat underlying cause (e.g., antifibrotics in pulmonary fibrosis) - Oxygen therapy if hypoxaemic.

Key Points for MRCP

1. **Obstructive**: Reduced FEV1/FVC; air trapping increases TLC and RV.
2. **Restrictive**: Normal/increased FEV1/FVC; all lung volumes reduced.
3. DLCO is useful to differentiate causes within each category:
   - **Obstructive**: DLCO decreased in emphysema, normal in asthma.
   - **Restrictive**: DLCO reduced in interstitial lung diseases, normal in extra-pulmonary causes.

Bronchial Asthma

Pathophysiology of Bronchial Asthma

Bronchial asthma is a chronic inflammatory disease characterised by airway hyperresponsiveness, inflammation, and obstruction. Below is a summarised overview of its pathophysiology:

Triggering Factors

- **Allergens:** Pollen, dust mites, animal dander.
- **Irritants:** Smoke, pollution.
- **Infections:** Viral upper respiratory tract infections.
- **Exercise:** Exercise-induced bronchospasm.
- **Medications:** Aspirin, beta-blockers.
- **Others:** Cold air, emotional stress.

Immunological Mechanisms

- **Initial Sensitisation:**
  - Exposure to allergen activates **dendritic cells**, leading to activation of **T-helper 2 (Th2) cells**.
  - Th2 cells release cytokines:
    - **IL-4:** Stimulates B-cell class switching to produce **IgE** antibodies.
    - **IL-5:** Attracts and activates eosinophils.
    - **IL-13:** Enhances mucus production and contributes to airway remodelling.
  - IgE binds to **mast cells**, sensitising them to future allergen exposure.
- **Re-Exposure:**
  - Allergen cross-links IgE on mast cells, causing **degranulation** and release of mediators.

Key Inflammatory Mediators

- **Early Phase:**
  - **Histamine:** Causes bronchoconstriction, increased vascular permeability, and mucus production.
  - **Leukotrienes (C4, D4, E4):** Potent bronchoconstrictors, increase vascular permeability.
  - **Prostaglandins (PGD2):** Contribute to bronchospasm.
- **Late Phase:**
  - Recruitment of eosinophils, neutrophils, and lymphocytes.
  - Release of additional mediators, such as **major basic protein (MBP)** from eosinophils, which causes epithelial damage.

Airway Changes

- **Bronchoconstriction:** Narrowing of airways due to smooth muscle contraction.
- **Airway Inflammation:** Increased oedema and immune cell infiltration.
- **Mucus Hypersecretion:** Excess mucus obstructs airways.
- **Airway Remodelling:**
  - Thickened basement membrane due to subepithelial fibrosis.
  - Hypertrophy and hyperplasia of airway smooth muscle.
  - Increased vascularity.

Airflow Obstruction

- Variable obstruction causes:
  - **Air trapping**: Difficulty exhaling, leading to hyperinflation.
  - **Reduced FEV1/FVC ratio** on spirometry.
  - V/Q mismatch, resulting in hypoxaemia.

Clinical Manifestations

- Episodic **wheezing, breathlessness, chest tightness**, and **cough**.
- Symptoms often worse at night or early morning and triggered by specific factors.

Diagnosis of Asthma: Step-by-Step (2024 Guidelines)

1. **Initial Assessment**
   - **Clinical History**:
     - Symptoms: wheezing, shortness of breath, chest tightness, cough, especially if they are variable, worsen at night or early morning, and are triggered by exercise, allergens, cold air, or viral infections.
     - Family history of asthma or other atopic conditions.
     - Occupational or environmental exposures
     - Personal medical history (e.g., eczema, allergic rhinitis).
2. **Physical Examination**:
   - Identify wheezing during normal breathing or forced expiration.
   - Assess for other signs such as nasal polyps or rhinitis which could suggest comorbid conditions.
3. **Objective Measurements**:
   - **Spirometry (Initial Test)**:
     - Measure Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC).
     - Check for reversible airflow limitation: Asthma is suggested by an increase in FEV1 of ≥12% and ≥200 mL after administration of a bronchodilator.
4. **Further Testing (If Needed)**:
   - **Bronchoprovocation Testing**:
     - Conduct if spirometry results are inconclusive and asthma is still suspected.
     - Methacholine or mannitol challenge tests can confirm airway hyperresponsiveness.
   - **Peak Expiratory Flow (PEF) Monitoring**:
     - Recommend if spirometry is unavailable.
     - Document PEF variability by measuring PEF over a period (e.g., twice daily for 2 weeks). Diurnal variability >10% suggests asthma.
5. **Additional Tests for Asthma Phenotyping**:
   - **Allergy Testing**:
     - Perform skin prick tests or specific IgE blood tests to identify potential triggers.
   - **Exhaled Nitric Oxide (FeNO)**:
     - Measure FeNO levels to identify eosinophilic airway inflammation (FeNO >25 ppb may support the diagnosis).

- **Blood Eosinophil Count**:
  - Elevated blood eosinophils can support the diagnosis, especially for phenotyping and assessing response to treatment.

6. **Differential Diagnosis**:
   - Rule out other conditions such as COPD, bronchiectasis, vocal cord dysfunction, and heart failure.
7. **Response to Treatment**:
   - An improvement in symptoms and lung function after initiating a trial of asthma treatment (e.g., inhaled corticosteroids) can also support the diagnosis.

Diagnosis (NICE guidelines- November 2024)

Clinical History

Aspect	Details
Symptoms	- Wheeze, noisy breathing, cough, breathlessness, or chest tightness. - Variation in symptoms (e.g., worse at night, early morning, or seasonally).
Triggers	- Any factors that worsen symptoms.
Family/Personal History	- History of asthma or allergic rhinitis.
Alternative Diagnoses	- Evaluate for symptoms suggesting other conditions (refer to BTS/SIGN guidelines).
Diagnosis Confirmation	- Do not confirm asthma without suggestive history and objective tests. - Code as "suspected asthma" until confirmed.
Identify Occupational Component	- Ask if symptoms are the same, better, or worse on days away from work, weekends, or holidays. - Refer patients with suspected occupational asthma to an occupational asthma specialist.

Physical Examination

Findings	Details
Primary Signs	- Expiratory polyphonic wheeze.
Considerations	- Normal examination does not exclude asthma.

Initial Treatment and Objective Tests

Action	Details
Immediate Treatment	- Treat acute symptoms immediately if unwell or highly symptomatic.
Objective Tests	- Perform **eosinophil count**, **FeNO**, **spirometry**, or **PEF** (pre- and post-bronchodilator).
Delayed Testing	- Conduct tests after acute symptoms are controlled if immediate testing is not possible.
Corticosteroid Impact	- Be aware that **spirometry** and **FeNO** may normalise with inhaled corticosteroid use.

Objective Tests for Diagnosing Asthma in Adults, Young People, and Children Aged 5–16

Test	Criteria for Diagnosis
Eosinophil Count	- Eosinophil count above laboratory reference range.
FeNO	- FeNO ≥ 50 ppb (adults).
Spirometry with BDR	- FEV1 increase ≥ 12% and ≥ 200 mL from pre-bronchodilator measurement. - FEV1 increase ≥ 10% of predicted normal value.
PEF Variability	- Measure twice daily for 2 weeks. - Variability ≥ 20% (amplitude percentage mean).
Bronchial Challenge Test	- Diagnose if **bronchial hyper-responsiveness** is present when other tests are inconclusive.

Objective Tests for Diagnosing Asthma in Children Aged 5–16

Step	Test	Criteria for Diagnosis
1. Initial Testing	FeNO (Fractional Exhaled Nitric Oxide)	- Diagnose if FeNO level is ≥ 35 ppb.
2. Spirometry with BDR	Bronchodilator Reversibility (BDR)	- Diagnose if FEV1 increase is ≥ 12% from baseline or ≥ 10% of the predicted normal value.
3. Peak Expiratory Flow (PEF)	PEF Monitoring	- Measure PEF twice daily for 2 weeks. - Diagnose if PEF variability is ≥ 20% (amplitude percentage mean).
4. Allergy Testing	Skin Prick Test or IgE/Eosinophil Count	- Exclude asthma if there is no sensitisation to house dust mite or IgE is normal. - Diagnose if there is evidence of sensitisation or IgE is raised, and eosinophil count > 0.5 x 10^9/L.
5. Specialist Referral	Paediatric Specialist Opinion	- Refer if diagnosis remains uncertain, including for bronchial challenge testing.

Positive Tests for Diagnosing Asthma (NICE Guidelines)

Test	Positive Criteria
Fractional Exhaled Nitric Oxide (FeNO)	- Adults: FeNO level ≥ 50 ppb. - Children (5–16 years): FeNO level ≥ 35 ppb.
Bronchodilator Reversibility (BDR)	- FEV1 increase ≥ 12% and ≥ 200 mL from pre-bronchodilator measurement. - Alternatively: FEV1 increase ≥ 10% of predicted normal value.
Peak Expiratory Flow (PEF)	- PEF variability ≥ 20% (measured twice daily for 2 weeks).
Eosinophil Count	- Blood eosinophil count above laboratory reference range (adults). - Children: Eosinophil count > 0.5 x 10^9/L.
Skin Prick or IgE Testing (Children)	- Sensitisation to house dust mite or raised total IgE level.
Bronchial Challenge Test	- Presence of bronchial hyper-responsiveness.

Management of asthma

Pharmacological Treatment Strategies

- **Preferred Stepwise Approach:**
    - **Step 1:** Low-dose inhaled corticosteroid (ICS) taken as needed with a short-acting beta-agonist (SABA) or low-dose ICS-formoterol for symptom relief.
    - **Step 2:** Low-dose ICS regularly or low-dose ICS-formoterol as needed.
    - **Step 3:** Low-dose ICS-long-acting beta-agonist (LABA).
    - **Step 4:** Medium-dose ICS-LABA or add-on therapy for uncontrolled symptoms.
    - **Step 5:** High-dose ICS-LABA and referral for specialist care; add-on treatments (e.g., biologics like anti-IgE, anti-IL5, or anti-IL4/IL13).

Non-Pharmacological Strategies

- **Education and Self-Management:**
    - Develop a personalized asthma action plan.
    - Regular follow-up visits to assess and adjust treatment.
- **Lifestyle Adjustments:**
    - Avoid triggers (e.g., allergens, smoke).
    - Encourage regular physical activity and weight management.
- **Vaccination:**
    - Recommend influenza and pneumococcal vaccines for patients

Drugs used in asthma

Drug	Mechanism of action	Notes
Salbutamol	Beta receptor agonist	• Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle through effects on beta 2 receptors • Used in asthma and chronic obstructive pulmonary disease (COPD). • Salmeterol has similar effects but is long-acting
Corticosteroids	Anti-inflammatory	• Inhaled corticosteroids are used as maintenance therapy • Oral or intravenous corticosteroids are used following an acute exacerbation of asthma or COPD
Ipratropium	Blocks the muscarinic acetylcholine receptors	• Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle • Used primarily in COPD • Tiotropium has similar effects but is long-acting
Methylxanthines (e.g. theophylline)	Non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP	• Given orally or intravenously • Has a narrow therapeutic index
Montelukast, zafirlukast	Blocks leukotriene receptors	• Usually taken orally • Useful in aspirin-induced asthma

Table showing examples of inhaled corticosteroid doses

Dose	Example
low dose	≤ 400 micrograms budesonide or equivalent
moderate dose	400 micrograms - 800 micrograms budesonide or equivalent
high dose	> 800 micrograms budesonide or equivalent

Omalizumab and Mepolizumab in the treatment of asthma

Characteristic	Omalizumab	Mepolizumab
Mechanism of Action	Anti-IgE monoclonal antibody; binds to free IgE, preventing it from binding to high-affinity receptors on mast cells and basophils, thus reducing allergic response	Anti-IL-5 monoclonal antibody; binds to IL-5, inhibiting its action and reducing eosinophil production and survival
Indication	Used in patients with moderate to severe allergic asthma not controlled with standard therapy (e.g., ICS-LABA); specifically for patients with elevated IgE levels and positive allergy testing	Used in patients with severe eosinophilic asthma with a high peripheral eosinophil count, not controlled with high-dose ICS-LABA
Patient Population	Typically used in patients with allergic asthma (atopy) and evidence of IgE-mediated sensitization	Recommended for patients with severe eosinophilic phenotype asthma, regardless of atopy
Route of Administration	Subcutaneous injection	Subcutaneous injection
Dosing Frequency	Every 2 to 4 weeks, based on weight and baseline IgE levels	Every 4 weeks
Clinical Benefits	Reduces frequency of exacerbations, improves symptom control, and may reduce oral corticosteroid use	Reduces exacerbation frequency, improves lung function, decreases oral corticosteroid use, and targets eosinophilic inflammation
Side Effects	Common: Injection site reactions, headache	Rare but serious: Anaphylaxis (requires monitoring after administration)
Monitoring Requirements	Observation for 2 hours after the initial 3 injections due to the risk of anaphylaxis; subsequent observations may be shorter	No specific post-administration observation needed, but monitoring for hypersensitivity is advised
Special Considerations	Approved for children 6 years and older	May be considered in patients with overlapping allergic and eosinophilic features

Classification of acute asthma exacerbation

1. Mild Acute Asthma Exacerbation

- **Symptoms**: Shortness of breath, mild wheezing, cough.
- **PEF (Peak Expiratory Flow)**: > 70% of predicted or personal best.
- **Ability to Talk**: Full sentences.
- **Use of Accessory Muscles**: Absent.
- **Heart Rate**: Normal or slightly elevated.
- **Oxygen Saturation (SpO2)**: ≥ 95%.

2. Moderate Acute Asthma Exacerbation

- **Symptoms**: More pronounced dyspnea and wheezing.
- **PEF**: 50–70% of predicted or personal best.
- **Ability to Talk**: Phrases or partial sentences.
- **Use of Accessory Muscles**: Present, but not significant.
- **Heart Rate**: Increased (100–120 bpm).
- **SpO2**: 91–94%.

3. Severe Acute Asthma Exacerbation

- **Symptoms**: Severe shortness of breath, inability to complete sentences.
- **PEF**: 33–50% of predicted or personal best.
- **Ability to Talk**: Words only, cannot complete sentences.
- **Use of Accessory Muscles**: Prominent, with visible intercostal and suprasternal retractions.
- **Heart Rate**: > 120 bpm.
- **Respiratory Rate**: > 30 breaths per minute.
- **SpO2**: < 90%.
- **Other Signs**: Agitation or restlessness may be present.

4. Life-Threatening Asthma Exacerbation

- **Symptoms**: Extreme breathlessness, patient is often unable to speak or may be silent (silent chest).
- **PEF**: < 33% of predicted or personal best.
- **Ability to Talk**: Unable to speak or one-word responses.
- **Use of Accessory Muscles**: Severe and pronounced.
- **Heart Rate**: Bradycardia or significant tachycardia (possible drop below 100 bpm as a late and ominous sign).
- **SpO2**: < 90% with cyanosis.
- **Mental State**: Confusion, drowsiness, or altered level of consciousness.
- **Other Signs**: Hypotension, pulsus paradoxus (a significant decrease in systolic blood pressure during inspiration).

Summary of Classification:

- **Mild**: PEF > 70%, full sentences, no accessory muscle use.
- **Moderate**: PEF 50–70%, speaks in phrases, some accessory muscle use.
- **Severe**: PEF 33–50%, speaks in words only, significant accessory muscle use, SpO2 < 90%.
- **Life-Threatening**: PEF < 33%, silent chest, altered consciousness, bradycardia, severe hypoxia.

Acute severe asthma

Moderate	Severe	Life-threatening
• PEFR 50-75% best or predicted • Speech normal • RR < 25 / min • Pulse < 110 bpm	• **PEFR 33 - 50%** best or predicted • Can't complete sentences in one breath • **RR > 25/min** • Pulse > 110 bpm	• PEFR < 33% best or predicted • **Oxygen sats < 92%** • PaO_2 < 8 kPa • Normal $PaCO_2$ (4.6-6.0 kPa) • Silent chest, cyanosis or feeble (Poor) respiratory effort • Bradycardia, dysrhythmia or hypotension • Exhaustion, confusion or coma

Management of acute severe asthma: Step-by-Step

1. **Immediate Oxygen Therapy:**
   - **Supplemental oxygen** to maintain SpO2 ≥ 94%.
   - Administer through a face mask or nasal cannula as needed.
2. **High-Dose Inhaled Bronchodilators:**
   - **Short-acting beta-agonists (SABA)**:
     - **Salbutamol** via a metered-dose inhaler (MDI) with spacer (4–10 puffs every 20 minutes for the first hour) or **nebulizer** (2.5–5 mg every 20 minutes for three doses).
   - **Ipratropium bromide**: Add 500 mcg via nebulizer or 8 puffs via MDI with spacer, especially in severe cases.
3. **Systemic Corticosteroids:**
   - **Oral or intravenous** corticosteroids should be administered early:
     - **Prednisolone** 40–50 mg orally for adults (or IV hydrocortisone if unable to take orally).
   - **Children**: 1–2 mg/kg of prednisolone, max 40 mg.
4. **Monitoring and Reassessment:**
   - Continuously assess clinical response every 15–30 minutes.
   - **Repeat PEF** measurements to monitor improvement.
   - Ensure close monitoring of vitals and mental state.
5. **Consider Adjunctive Therapies:**
   - **Magnesium sulfate IV** (2 g over 20 minutes) for patients not responding to initial treatment.
   - **Aminophylline**: Can be considered if severe bronchospasm persists despite initial therapy.
6. **Hydration and Electrolyte Management:**
   - Maintain adequate hydration but avoid excessive fluid administration.
   - Monitor electrolytes, particularly potassium levels, due to SABA use.
7. **Mechanical Ventilation:**
   - **Indications**: Worsening hypoxemia, hypercapnia, exhaustion, or altered mental status.
   - **Non-invasive ventilation (NIV)**: Consider for patients with respiratory distress if they can tolerate it.
   - **Invasive ventilation**: If respiratory failure persists or worsens.

Pharmacological Management of Asthma in People Aged 12 and Over
Initial Management (NICE guidelines- November 2024)

Condition	Recommendation
Newly Diagnosed Asthma	- Offer **low-dose inhaled corticosteroid (ICS) and formoterol combination inhaler** as needed (**Anti-Inflammatory Reliever (AIR) therapy**).
	- Use licensed **budesonide/formoterol inhalers** (other ICS/formoterol inhalers are off-label).
Highly Symptomatic or Severe Exacerbation	- Start **low-dose Maintenance and Reliever Therapy (MART)** (combined ICS and formoterol inhaler for maintenance and as-needed relief). - Treat acute symptoms with additional therapies, such as a course of oral corticosteroids if indicated. - Consider stepping down to AIR therapy once asthma is controlled.

Medicine Combination and Sequencing

Condition	Recommendation
Asthma Not Controlled on Low-Dose ICS/Formoterol (as-needed)	- Offer **low-dose Maintenance and Reliever Therapy (MART)**.
Asthma Not Controlled on Low-Dose MART	- Step up to **moderate-dose Maintenance and Reliever Therapy (MART)**.
Asthma Not Controlled on Moderate-Dose MART	- Check **Fractional Exhaled Nitric Oxide (FeNO)** level and **blood eosinophil count**: - Refer to a specialist in asthma care if levels are raised. - If FeNO and eosinophil levels are normal, trial either: **- Leukotriene Receptor Antagonist (LTRA)**: Oral medication that blocks leukotrienes. - Long-Acting Muscarinic Antagonist (LAMA): Inhaled medication that relaxes airway smooth muscle. Adjust based on response after 8–12 weeks: 1- Controlled: **Continue treatment.** 2- Improved but Inadequate: **Continue current therapy and add the other medicine (LTRA or LAMA).** 3- No Improvement: **Switch to the alternative medicine (LTRA or LAMA).**
Asthma Not Controlled Despite Moderate-Dose MART and Trials of LTRA/LAMA	- Refer to a specialist in asthma care.

Transferring from Other Treatment Pathways

Condition	Recommendation
Using Short-Acting Beta2 Agonist (SABA) Only	- Change to **low-dose ICS/formoterol as-needed AIR therapy**.
Uncontrolled on Regular Low-Dose ICS with SABA as Needed	- Change to **low-dose Maintenance and Reliever Therapy (MART)**. Includes patients on regular low-dose ICS combined with either: - SABA (Short-Acting Beta2 Agonist) as needed. - Long-Acting Beta2 Agonist (LABA) with SABA as needed.
	- Includes patients on regular low-dose ICS combined with either: - Leukotriene Receptor Antagonist (LTRA) with SABA as needed.
Uncontrolled on Regular Moderate-Dose ICS with SABA as Needed	- Change to **moderate-dose Maintenance and Reliever Therapy (MART)**. - Includes patients on regular moderate-dose ICS with any combination of SABA, LABA, LTRA, or LAMA.
Switching to MART	- Evaluate whether to stop or continue supplementary therapies (e.g., LTRA, LAMA) based on benefit.
Uncontrolled on High-Dose ICS	- Refer to a specialist in asthma care.

Monitoring Asthma Control

Aspect	Details
Regular Review	**Monitor asthma control at every review by assessing:** - Time off work or school due to asthma. - Reliever inhaler use (check prescription records). - Number of oral corticosteroid courses. - Hospital admissions or emergency department visits due to asthma.
Validated Questionnaires	- Consider tools like the **Asthma Control Questionnaire**, **Asthma Control Test**, or **Childhood Asthma Control Test**.
Peak Expiratory Flow (PEF)	- Avoid regular PEF monitoring unless necessary for specific reasons (e.g., part of a personalised asthma action plan).
Fractional Exhaled Nitric Oxide (FeNO)	**Use FeNO monitoring in adults:** - At regular reviews. - Before and after changes in asthma therapy.

Asthmatic patient with + $PaCO_2$ at the upper limit of normal. What would be the most appropriate next step?

- ⇨ **A normal or elevated pCO_2 in an asthmatic indicates impending respiratory failure**
- ⇨ review by an anaesthetist/intensivist is the next immediate step.
- ⇨ Hypercapnia and signs of fatigue are indications for immediate intubation and ventilation.

Magnesium sulphate - monitor reflexes + respiratory rate

Omalizumab
- **anti-IgE monoclonal antibody**
- **used for resistant asthma with evidence of raised IgE and allergic symptoms.**

Mepolizumab
- **anti-IL5** monoclonal antibody
- **used for resistant asthma with raised eosinophils**

B-blockers, including eye drops, should be avoided in patients with asthma. They are not, however, absolutely contraindicated.

Chronic Obstructive Pulmonary Disease(COPD)

Definition: airflow obstruction that is not fully reversible.

Epidemiology:
- worldwide prevalence of 10%
- COPD is the third leading cause of death worldwide

Subtypes of COPD
1. **Chronic bronchitis:** defined as chronic cough and sputum production for at least three months of two consecutive years in the absence of other disease which could explain these symptoms.
2. **Emphysema**

Pathophysiology
- Inflammatory changes → ciliary dysfunction and **increased goblet cell size and number**, → excessive mucus secretion.
  - **Increased airway resistance** is the physiological definition of COPD.
  - Decreased elastic recoil, fibrotic changes in lung parenchyma, and luminal obstruction of airways by secretions all contribute to increased airways resistance.
  - Progressive hypoxia → vascular smooth muscle thickening → pulmonary hypertension

Causes
- Smoking
- Alpha-1 antitrypsin deficiency
- Using open fires at homes for cooking or heating (patients from the developing world present with a COPD-like history without smoking history)
- Occupational exposures, such as harmful dust and chemicals

Emphysema
- **Definition**
  - ⇨ emphysema is a pathological term indicating enlargement of the airspaces distal to the terminal bronchioles that is accompanied by destruction of the airspace walls

- **Pathophysiology**
  - ⇨ destruction of alveolar air sacs due to an **imbalance between protease and anti-protease action.**
  - ⇨ **loss of elastic recoil, which drives airflow limitation.**

Types of emphysema

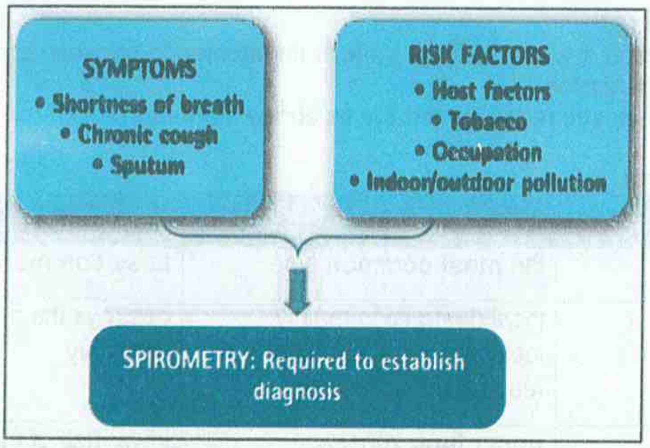
Type	Centriacinar (centrilobular)	Panacinar
Prevalence	the **most common** type	**Less common**
destruction	focal destruction mainly localized to the proximal respiratory bronchioles	destroys the entire alveolus uniformly
Location	**upper lung** zones.	lower half of the lungs.
causes	**smoking** & dust	**alpha 1-antitrypsin (AAT) deficiency**

Features and complications

- Chronic cough , SOB and recurrent infection
- extensor plantar response is common in (COPD) **due to carbon dioxide retention, which results in carbon dioxide narcosis.**
- Cor pulmonale
  - ⇨ features include peripheral oedema, raised jugular venous pressure, systolic parasternal heave, loud P2
  - ⇨ use a loop diuretic for oedema, consider long-term oxygen therapy
  - ⇨ ACE-inhibitors, calcium channel blockers and alpha blockers are not recommended by NICE
- Polycythaemia

Investigation and diagnosis

- **spirometry**
  - ⇨ Post-bronchodilator spirometry to demonstrate airflow obstruction: FEV1/FVC ratio less than 70%
- **Chest x-ray**
  - ⇨ hyperinflation, bullae, flat hemidiaphragm.
  - ⇨ Also, important to exclude lung cancer
- **Full blood count:** exclude secondary polycythaemia
- **methacholine challenge**
  - ⇨ useful in differentiating between asthma and chronic obstructive pulmonary disease (COPD).
  - ⇨ methacholine utilizes the M3 receptor for bronchoconstriction.
- **ABG**
  - ⇨ In long standing COPD the bicarbonate is likely to be normal, or raised if the patient has chronic hypercapnia. (a low pH, low pO_2, high pCO_2 and a high HCO_3)



Severity of COPD: categorised by using the FEV1:

Post-bronchodilator FEV1/FVC	FEV1 (of predicted)	Severity
< 0.7	> 80%	Stage 1 - Mild
< 0.7	**50-79%**	**Stage 2 - Moderate**
< 0.7	**30-49%**	**Stage 3 - Severe**
< 0.7	< 30%	Stage 4 - Very severe

Causes of acute exacerbations

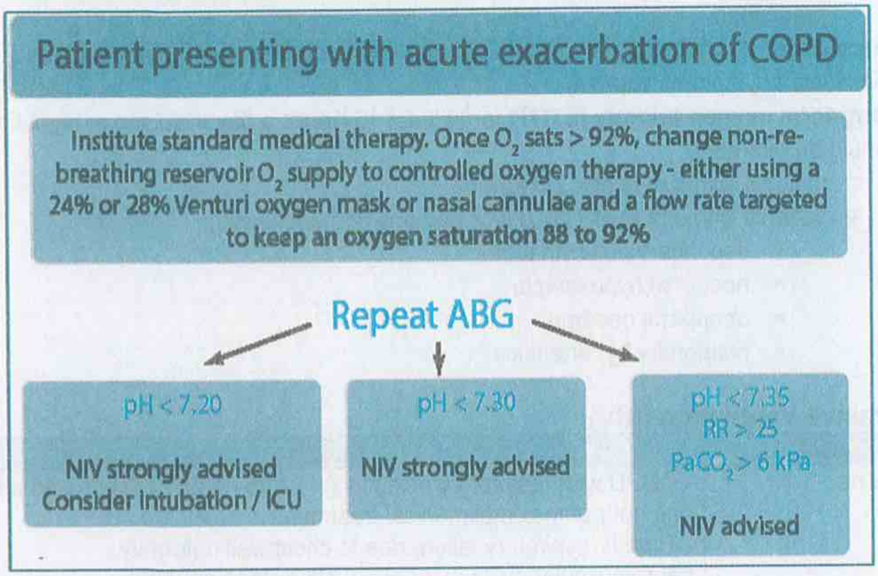
- Infective exacerbation of COPD is **the most common cause of haemoptysis in UK patients**
- Bacterial organisms
  - ⇨ *Haemophilus influenzae* **(most common cause of COPD exacerbation)**
  - ⇨ *Streptococcus pneumoniae*
  - ⇨ *Moraxella catarrhalis*
- Respiratory viruses : account for around 30% of exacerbations, with the **human rhinovirus** being the most important pathogen.

Management of acute exacerbations

- **Bronchodilator**
- **Steroids:** prednisolone 30 mg daily for 7-14 days. Prolonged courses offer no additional benefit
- **Antibiotics:** It is common practice for all patients with an exacerbation of COPD to receive antibiotics. NICE do not support this approach. They recommend giving oral antibiotics 'if sputum is purulent or there are clinical signs of pneumonia'
- **Oxygen management of COPD patients**
  - ⇨ **If the patient have an individual target** range: Oxygen should be given to maintain SaO2 within the **patient's individual target** range, if available
  - ⇨ **If the individual target is not known:**
    - prior to availability of blood gases (pCO2 is unknown):

- saturations should be maintained at 88-92% to avoid risk of hypercapnia
    - after availability of blood gases (**pCO2 is normal**): adjust target range to 94-98%

- **Non-invasive ventilation (NIV)**
    - BiPAP is the modality of choice for treating CO2 retention.
    - Indicated for hypercapnic respiratory failure (pH < 7.35).
    - Improves gas exchange, reduces intubation rates and mortality.
- **Invasive ventilation**
    - Reserved for patients not responding to NIV.
    - Used in cases of severe respiratory acidosis, altered mental status, or hemodynamic instability.
    - If the pH is below 7.25.



Management of stable COPD

- **General management**
    - ⇨ smoking cessation advice
    - ⇨ annual influenza vaccination
    - ⇨ one-off pneumococcal vaccination

Pharmacological therapy

- **First-line:**
    - ⇨ short-acting beta2-agonist (SABA) or short-acting muscarinic antagonist (SAMA)
- **Second-line:**
    - ⇨ for patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by the FEV1
        - FEV1 > 50%
            - long-acting beta2-agonist (LABA), for example salmeterol, or:

- long-acting muscarinic antagonist (LAMA), for example tiotropium
- FEV1 < 50%
  - LABA + inhaled corticosteroid (ICS) in a combination inhaler, or:
  - LAMA

- **Third-line:**
  - For patients with persistent exacerbations or breathlessness
    - if taking a LABA then switch to a LABA + ICS combination inhaler
    - otherwise give a LAMA and a LABA + ICS combination inhaler

Other pharmacological therapies

- **Oral theophylline**
  - NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot used inhaled therapy
  - the dose should be reduced if macrolide or fluoroquinolone antibiotics are co-prescribed
- **Mucolytics:** should be 'considered' in patients with a chronic productive cough and continued if symptoms improve
- **Long-term oxygen therapy (LTOT)** for at least **15 hours** a day including at night time: should be offered to:
  - patients with a pO2 of < 7.3 kPa or
  - patients with a pO2 of 7.3 - 8 kPa and one of the following:
    - secondary polycythaemia
    - nocturnal hypoxaemia
    - peripheral oedema
    - pulmonary hypertension

Non-Invasive Ventilation (NIV)

Aspect	Details
Indications	- COPD with respiratory acidosis (pH 7.25–7.35) not improved after one hour of maximal medical treatment. - Type II respiratory failure due to chest wall deformity, neuromuscular disease, or obstructive sleep apnoea. - Cardiogenic pulmonary oedema. - Weaning from tracheal intubation.
Advantages	- Reduces intubation rates. - Lowers hospital mortality rates. - Shortens hospital stays.
Initial Settings (COPD)	- **IPAP:** 10 cm H2O (RCP) or 12–15 cm H2O (BTS). - **EPAP:** 4–5 cm H2O. - **Backup rate:** 15 breaths/min. - **Inspiration: Expiration ratio:** 1:3.
Monitoring and Adjustments	- Repeat ABGs after 1 hour of NIV and after any setting change. - **IPAP adjustments:** Gradually increase by 2–5 cm H2O every 10 minutes (target: 20 cm H2O). - Specialist advice required for EPAP changes.

Aspect	Details
Managing Mask Intolerance	- Use haloperidol or morphine to improve tolerance. - Decreasing IPAP or stopping NIV is inappropriate as it increases hypoxia and acidosis. - Diazepam is contraindicated.
Complications	- Ventilation-associated pneumothorax (acute presentation). - Ventilator-associated pneumonia (prolonged ventilation).
Contraindications	- **Absolute:** Inability to fit the NIV mask, cardiopulmonary arrest, need for urgent intubation. - **Relative:** Haemodynamic instability requiring inotropes/pressors (except in critical care), confusion/agitation.
NIV Modes	- **CPAP:** Provides continuous positive pressure, effective for hypoxaemic respiratory failure by recruiting alveoli and increasing functional residual capacity. - **BiPAP:** Provides IPAP and EPAP, effective for both hypoxaemic and hypercarbic respiratory failure.
Minute Ventilation	- Equal to tidal volume × respiratory rate. - Decreasing tidal volume or respiratory rate reduces minute ventilation, increasing CO_2 retention (used in managing metabolic alkalosis).

Long-Term Oxygen Therapy (LTOT)

Aspect	Details
Indication in COPD	LTOT recommended if **2 measurements of pO_2 < 7.3 kPa**.
Patients to Assess for LTOT	- Very severe airflow obstruction (FEV1 < 30% predicted). - Cyanosis. - Polycythaemia. - Peripheral oedema. - Raised jugular venous pressure. - Oxygen saturations ≤92% on room air.
Assessment for LTOT	- Measure arterial blood gases on 2 occasions at least 3 weeks apart in stable COPD patients on optimal management. - Perform blood gases at least 4 weeks after exacerbation.
Indications for LTOT in COPD	- pO_2 < 7.3 kPa. - pO_2 between 7.3–8.0 kPa with one of the following: • Secondary polycythaemia. • Nocturnal hypoxaemia. • Peripheral oedema. • Pulmonary hypertension.
Duration of LTOT	At least 15 hours/day, including night-time use.
Contraindications	Continued cigarette smoking is a relative contraindication.
Prescription Criteria	- Prescribe LTOT if PaO_2 is consistently ≤7.3 kPa in clinical stability (defined as no exacerbation for 5 weeks). - $PaCO_2$ level does not influence LTOT prescription.
Managing Respiratory Acidosis	- LTOT with nocturnal BiPAP is required if respiratory acidosis ($PaCO_2$ rise >1 kPa) is observed on 2 stable assessments. - BiPAP is the modality of choice for CO_2 retention.
Prognostic Impact	LTOT, used for at least 15 hours/day, is the only treatment that improves long-term prognosis in COPD.

Lung Volume Reduction Surgery (LVRS)

Aspect	Details
Definition	Palliative treatment for advanced COPD involving removal of the least functional parts of the lungs.
Beneficial Groups	- **Group 1:** Upper lobe emphysema, low exercise capacity: Improved functional outcomes and survival compared to medical therapy. - **Group 2:** Upper lobe emphysema, high exercise capacity: Improved functional outcomes but no survival benefit. - **Group 3:** Non-upper lobe emphysema, low exercise capacity: Improved survival but no functional outcome difference.
High-Risk Groups	- Non-upper lobe emphysema, high exercise capacity. - Extremely poor pulmonary function (FEV1 ≤20% predicted) with either: - Homogenous emphysema on CT. - Carbon monoxide diffusing capacity (DLCO) ≤20% predicted.
Indications	- CO_2 retention (pCO_2 ≤7.3). - Severe exercise limitation despite maximal therapy. - Predominant upper lobe emphysema with persistent symptoms after pulmonary rehabilitation.
Selection Criteria	- Age <75 years. - Clinical diagnosis of emphysema. - Ex-smoker for >4 months. - Stable on ≤20 mg prednisolone daily. - Significant limitation despite 6–12 weeks of pulmonary rehabilitation on optimal medical therapy. - Compliance with medical regimen. - FEV1 >20% predicted. - Post-bronchodilator FEV1 >45% predicted (>15% if age >70). - Hyperinflation (TLC >100% and RV >150% predicted). - DLCO >20% predicted. - 6MWD >140 m after rehabilitation. - Low exercise capacity post-rehabilitation. - HRCT: Bilateral severe emphysema, ideally upper-lobe predominant.

Prognosis of COPD

- Once respiratory failure criteria have been met, the 5-year survival rate is only around 25%.
- **Prognostic indicators in COPD**
  - ⇨ **The strongest predictors of survival in patients with (COPD) are FEV1**
- **Factors which may improve survival in patients with stable COPD**
  - ⇨ **smoking cessation. the single most important intervention in patients who are still smoking**
  - ⇨ **long term oxygen therapy** in patients who fit criteria
  - ⇨ lung volume reduction surgery in selected patients

The only treatment that improves the long-term prognosis in patients with (COPD) is LTOT, given for at least 15 hours per day.

COPD - reason for using inhaled corticosteroids - reduced exacerbations

COPD - still breathless despite using inhalers as required?
- FEV1 > 50%: LABA or LAMA
- FEV1 < 50%: LABA + ICS or LAMA

COPD - LTOT if 2 measurements of pO2 < 7.3 kPa

Factors to consider when initiating inhaled corticosteroids (ICS) for COPD (GOLD guidelines January 2021)

Strong support	Consider use	Against use
▪ History of hospitalization for exacerbation of COPD ▪ ≥ 2 moderate exacerbation of COPD per year ▪ Blood eosinophils > 300 cells/ml ▪ History of, or concomitant asthma	▪ 1 moderate exacerbation of COPD per year ▪ Blood eosinophils 100 – 300 cells/ml	▪ Repeated pneumonia events ▪ Blood eosinophils < 100 cells/ml ▪ History of mycobacterial infection

PassOnExam

Pulmonary embolism (PE)

Pathophysiology

- Decreased lung blood flow leads to ventilation-perfusion mismatches (normal ventilation but reduced perfusion), causing increased physiological dead space.

Risk Factors

- **Virchow Triad Components**:
  1. **Hypercoagulability**: Thrombophilia (e.g., factor V Leiden mutation), pregnancy, use of oral contraceptives.
  2. **Endothelial Damage**: Inflammatory or traumatic, activating clotting factors.
  3. **Stasis**: Varicosis, immobilization.
- **Major Risk Factors**: Lower limb issues (e.g., fractures, varicose veins), postoperative ICU stay, hospitalization, abdominal/pelvic malignancy, history of VTE, pregnancy.
- **Minor Risk Factors**: Occult malignancy, long-distance travel, hypertension, cardiac failure, oral contraceptive use.

Clinical Features

- **Common Symptoms**: Sudden dyspnea, pleuritic chest pain, haemoptysis.
- **Signs**: Tachypnea (>16/min), tachycardia (>100 bpm), fever (>37.8°C).

Diagnosis

- **Initial Assessment**: Chest X-ray to exclude other conditions.
- **Wells Score**:
  - 4 points: PE likely → immediate CTPA.
  - ≤4 points: PE unlikely → perform D-dimer test.
- **Definitive Investigations**:
  - **CT Pulmonary Angiogram (CTPA)**: First-line diagnostic tool.
  - **V/Q Scan**: Used when CTPA is contraindicated (e.g., renal impairment).
  - **D-dimers**: High sensitivity but low specificity; useful for ruling out PE in low-risk patients.
  - **ECG Findings**: Sinus tachycardia, S1Q3T3 pattern, right bundle branch block.

Management

- **Anticoagulation**:
  - **First-line**: Apixaban or Rivaroxaban.
  - **Alternatives**: LMWH followed by dabigatran or edoxaban, or warfarin.
  - **Duration**: 3 months for most cases; longer for active cancer or unprovoked PE.
- **Thrombolysis**: Indicated for massive PE with hemodynamic instability (e.g., alteplase).
- **IVC Filters**: Consider if anticoagulation is contraindicated or fails.

Special Considerations

- **PE in Pregnancy**:
  - Use **LMWH** as first-line treatment.
  - **CTPA vs. V/Q Scan**: CTPA preferred for abnormal chest X-ray, V/Q scan has lower risk of childhood cancer.
  - **D-dimer**: Limited utility due to natural elevation during pregnancy.
- **Post-thrombotic Syndrome (PTS)**: Prevention with prolonged LMWH use (>12 weeks).

Recurrent PE Considerations

- Associated with genetic predispositions (e.g., antithrombin III deficiency, protein C deficiency).
- Inferior vena caval filters may be considered for recurrent PE despite anticoagulation.

Wells Score

Clinical Feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

Clinical Probability Simplified Scores

Clinical Probability	Score
PE likely	More than 4 points
PE unlikely	4 points or less

Pulmonary embolism in pregnancy: diagnosis and management

Diagnosis:

- **Initial tests:** Chest X-ray and ECG to rule out other causes (e.g., pneumonia, pneumothorax).
- **If chest X-ray is normal:**
  - **With DVT signs/symptoms:** Perform compression duplex Doppler of both legs. A positive result suggests treatment with full-dose LMWH (warfarin is contraindicated in pregnancy).
  - **Without DVT signs/symptoms:** Perform a V/Q lung scan or CTPA.
- **If chest X-ray is abnormal with suspected PE:** CTPA is preferred over V/Q scan.
- **CTPA vs. V/Q Scan:**
  - **CTPA:** Higher maternal breast cancer risk.
  - **V/Q Scan:** Higher childhood cancer risk.
- **D-dimer:** Limited diagnostic value as it is often elevated during pregnancy..

Treatment of PE in pregnancy

Initial Management

- **Immediate Action**: Start **low-molecular-weight heparin (LMWH)** immediately in clinically suspected DVT or PE until diagnosis is excluded.
- **First-line Treatment**: Continue **LMWH** throughout pregnancy and for at least 6 weeks postnatally, ensuring a total treatment duration of at least 3 months.
- **Second-line Options**: If **LMWH** or **unfractionated heparin (UFH)** is not tolerated, use alternative anticoagulants like **fondaparinux**, **argatroban**, or **r-hirudin**.

Special Situations

- **Unfractionated Heparin (UFH)**: Preferred for **massive PE** with cardiovascular compromise; monitor platelet count every 2–3 days from days 4–14 or until discontinued.
- **Warfarin**: Avoid during pregnancy. Postpartum use should be delayed until at least the fifth day, and longer if the risk of postpartum hemorrhage is high.

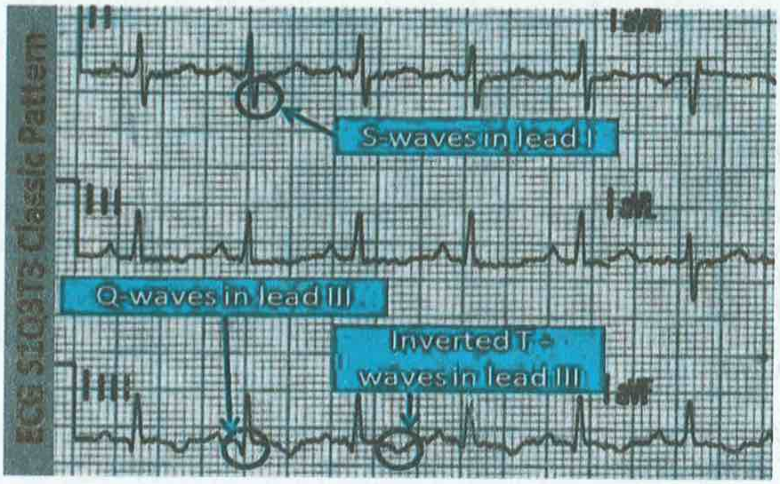
Post-thrombotic Syndrome (PTS)

- **Prevalence**: Affects nearly 50% of patients post-DVT.
- **Features**: Chronic leg pain, swelling, redness, and ulcers.
- **Prevention**: Prolonged use of **LMWH** for more than 12 weeks.

PE: Sudden shortness of breath, pleuritic chest pain with haemoptysis and tachypnoea are the commonest features. (triad of pleuritic chest pain, dyspnoea and haemoptysis)

Start low molecular weight heparin and request CT pulmonary angiography **if the symptoms and findings clearly point towards pulmonary embolism (PE).**

Pulmonary embolism - CTPA is first-line investigation



Massive PE + hypotension - thrombolyse

Fat embolism

Definition: Entry of fat particles usually from bone marrow, in the pulmonary circulation.

Causes

- Traumatic (95%):
  - ⇨ **most commonly associated with long bone (especially femur) and pelvic fractures.** typically manifests 24 to 72 hours after the initial insult.
- Non-traumatic (Rare): Sickle cell crisis, pancreatitis, osteomyelitis.

Features

- The classic triad of **hypoxemia**, **neurologic abnormalities** (eg, confusion, altered consciousness, seizure), and a **petechial rash**.
- Less common: anemia, thrombocytopenia, fever, lipiduria, and coagulation abnormalities;
- Rare: myocardial depression and shock

Diagnosis

- Presence of clinical triad
- Exclusion of other possible causes
  - ⇨ embolization syndromes (thrombus, amniotic fluid, tumor, foreign body, air),
  - ⇨ acute alveolar filling diseases (eg, heart failure, pneumonia, and ARDS) and
  - ⇨ cutaneous vasculitic disorders (eg, systemic lupus erythematosus).

Treatment

- **Supportive**
  - ⇨ Intravenous (iv) fluids to maintain high right ventricular filling pressures.
  - ⇨ High flow oxygen
  - ⇨ Diuretic treatment would be strongly contraindicated in this case. This is because right ventricular output is dependent on elevated filling pressures. Reducing the preload is therefore not a good idea.
- Steroids are reserved for severe or refractory cases.
- Most patients fully recover spontaneously.

The diagnosis of cholesterol embolism should be considered in any patient with atherosclerotic disease presenting with deteriorating renal function, multisystem disease or distal ischaemia developing after an invasive arterial procedure.
The classic triad of presentation are Eosinophilia, Acute renal failure and Livedo reticularis.

Aspergillosis

Comparison of Aspergillosis Types

Type	Definition & Pathophysiology	Clinical Features	Diagnosis	Treatment
Allergic Bronchopulmonary Aspergillosis (ABPA)	Hypersensitivity reaction to Aspergillus colonization in the airways. Common in patients with asthma or cystic fibrosis.	Recurrent wheezing, cough, fever, mucus plugs, bronchiectasis, and eosinophilia.	Elevated total IgE, positive Aspergillus-specific IgE, positive skin test, CXR/CT showing bronchiectasis.	Corticosteroids and antifungal agents (e.g., itraconazole).
Aspergilloma (Fungal Ball)	Colonization of a pre-existing lung cavity (e.g., from TB or sarcoidosis) by Aspergillus.	Often asymptomatic; may present with hemoptysis.	CXR/CT showing a mobile, intracavitary mass with an "air crescent" sign.	Observation if asymptomatic; surgical resection or antifungal therapy if hemoptysis occurs.
Chronic Pulmonary Aspergillosis (CPA)	Progressive lung disease with chronic colonization of Aspergillus in damaged lung tissue.	Chronic cough, weight loss, fatigue, hemoptysis.	Imaging showing cavities with/without fungal balls, positive Aspergillus antibodies.	Long-term antifungal therapy (e.g., itraconazole, voriconazole).
Invasive Aspergillosis	Occurs in immunocompromised patients (e.g., neutropenia, post-transplant). Fungal invasion of lung parenchyma and blood vessels.	Fever, chest pain, cough, hemoptysis, and signs of systemic infection.	High-resolution CT showing nodules with "halo sign," positive galactomannan antigen, biopsy for confirmation.	Voriconazole or other systemic antifungals; aggressive treatment required.
Aspergillus Sinusitis	Non-invasive or invasive sinus infection by Aspergillus species.	Nasal congestion, discharge, facial pain, potential orbital invasion in invasive forms.	Nasal endoscopy, CT scan, fungal culture.	Surgical debridement and antifungal therapy for invasive cases; topical therapy for non-invasive forms.

The most important diagnostics for the different aspergillosis types are:

- **ABPA: increased IgE and eosinophil count.**
- **Aspergilloma: positive culture or serology and fungus ball seen on chest imaging.**
- **Invasive aspergillosis: positive culture or biopsy showing septate hyphae.**

Summary Points:

- **ABPA**: Associated with hypersensitivity in patients with asthma/CF.
- **Aspergilloma**: Fungal ball in pre-existing cavities; may cause hemoptysis.
- **CPA**: Chronic lung disease with long-term Aspergillus colonization.
- **Invasive Aspergillosis**: A medical emergency in immunocompromised patients with high mortality.
- **Aspergillus Sinusitis**: Can range from benign to invasive with potential complications.

Allergic bronchopulmonary aspergillosis (ABPA)

Definition

- **ABPA** results from an allergy to Aspergillus spores (<u>**Type I hypersensitivity**</u> **to Aspergillus fumigatus**).
- a hypersensitivity reaction caused by exposure to Aspergillus that mostly occurs in patients with cystic fibrosis or asthma
- Aspergillus fumigatus is the most common airborne fungus causative organism for ABPA.

Risk factors

- Preexisting bronchopulmonary conditions (e.g., **asthma**, **cystic fibrosis**)

Features

- Bronchoconstriction: wheeze, cough, dyspnoea (clinical deterioration in asthma symptoms)
- Bronchiectasis (**proximal**)

Investigations

- Serum **eosinophilia**
- Raised IgE: helpful test, but **not specific** enough to establish the diagnosis.
- **Aspergillus skin-prick test** <u>**(the most specific investigation)**</u>
  - ⇨ Positive radioallergosorbent (RAST) test to Aspergillus.
  - ⇨ Immediate (type I) reactions occur in virtually all patients with ABPA following intradermal injections of *Aspergillus fumigatus* extracts, with only 16% developing delayed (type IV) reactions.
  - ⇨ **An early positive skin-prick test for Aspergillus fumigatus is the <u>most specific</u> to (ABPA).**
  - ⇨ Positive skin-prick tests reflect antigen-specific IgE.
- **Positive IgG precipitins** (not as positive as in aspergilloma) <u>in 70% of patients</u>.
  - ⇨ <u>**Precipitins (IgG) are more usual with an aspergilloma**</u>, but may be positive in ABPA or in up to 10% of patients with asthma.
- Pulmonary infiltrates on CXR. Lobar collapse can also occur, due to mucus plugging.

Management

- First line →steroids (prednisone)
- **Second line → add itraconazole** or voriconazole
  - ⇨ Itraconazole leads to significant reductions in corticosteroid dose, decreases IgE levels, greater resolution of pulmonary infiltrates, and improves exercise tolerance.

Allergic bronchopulmonary aspergillus: both of the following must be present to confirm the diagnosis:
- 🕮 Aspergillus skin test positivity or detectable IgE levels against aspergillus fumigatus **and**
- 🕮 Elevated total serum IgE concentration.

Aspergilloma

Definition

- An aspergilloma is a mycetoma (**mass-like fungus ball**) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer, cystic fibrosis or emphysema)

Feature

- often asymptomatic
- cough
- **haemoptysis** in up to three quarters of patients (may be severe and fatal)
- Systemic symptoms of weight loss, lethargy and fever are less common.

Investigations

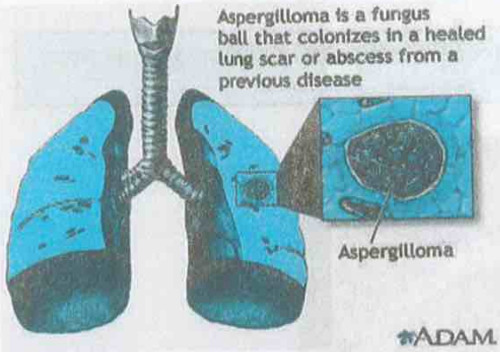
- chest x-ray containing a rounded opacity within a cavity often associated with a rim of air. These features are seen more clearly on **CT**.
- High titres Aspergillus precipitins (**IgG** antibodies) present in 95% of cases.

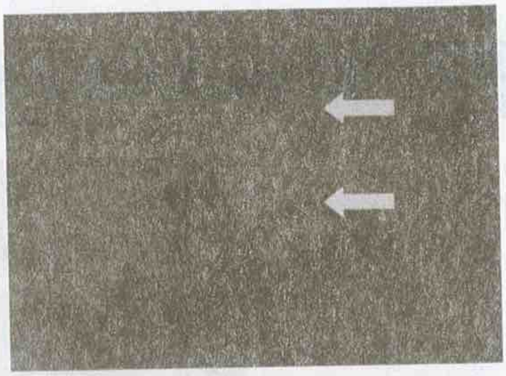
Treatment

- **Surgery should be considered as a first-line** option where erosion into a major vessel and massive haemoptysis is a possibility
- **In case of massive haemoptysis the next appropriate management – after transfusion and resuscitation- is → Angiography and embolisation, after that → lobar resection as the intervention of next resort**

Aspergilloma should be considered in patients with chronic lung disease and radiographs showing intracavitary mass lesions.

The clue can be a lack of improvement with broad spectrum intravenous antibiotics, haemoptysis and chest X-Ray findings.





Invasive aspergillosis (IA)

Definition

- a severe form of *Aspergillus* infection with severe pneumonia and septicemia, most commonly occurs in immunocompromised individuals.

Risk factors

- **immunosuppression** (e.g., due to HIV/**chemotherapy**, after organ transplantation) or neutropenia (e.g., due to chronic granulomatous infection).

Features

- Symptoms of active infection & haemoptysis.

Investigations

- the classical signs on CT scanning the **'halo sign' air crescent sign**
- galactomannan test:
  - ⇨ Galactomannan is a component of the cell wall of the *Aspergillus* and is released during growth.
  - ⇨ Detection of galactomannan in blood by ELISA is used to diagnose invasive aspergillosis
- Silver staining shows → hyphae.
  - ⇨ **Haematoxylin and eosin (H&E) stain** does not stain most of the fungi, except the **Aspergillus** species.

Treatment

- 1st line **voriconazole:** start iv before oral (as oral 10 days to get therapeutic levels).
- 2nd line (If voriconazole is not tolerated): **amphotericin B**

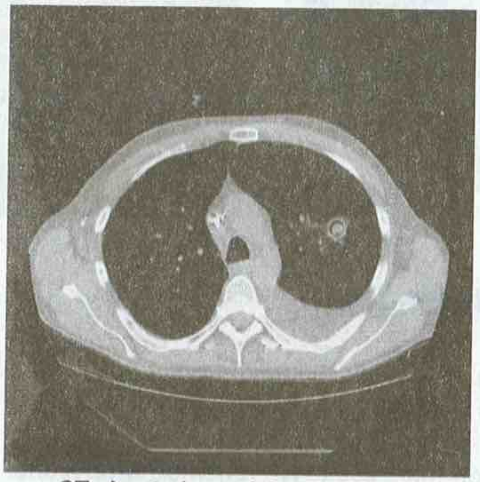
Prognosis

- Mortality vary from 40-90%

Invasive aspergillosis

- **Invasive aspergillosis should be suspected in someone who is immunocompromised (neutropenia, steroids, HIV) with severe chest pain, high-grade fevers, and haemoptysis.**
- **The treatment of choice for invasive aspergillosis is voriconazole**

Voriconazole → ↑risk of developing skin malignancy (malignant melanoma, squamous cell carcinoma)



CT chest showed Aspergilloma

Alpha-1 antitrypsin (A1AT) deficiency

Definition: A genetic disorder characterized by defective alpha-1 antitrypsin (A1AT) enzyme accumulation, affecting the lungs and liver.

Genetics & Pathophysiology:

- **Inheritance**: Autosomal co-dominant.
- **Gene**: Mutations in the SERPINA1 gene on chromosome 14.
- **Function**: A1AT inhibits neutrophil elastase, preventing lung damage.
- **Key Genotypes**:
  - PiMM: Normal A1AT levels.
  - PiZZ: Severe deficiency (~10-15% normal levels).
- **Effects**:
  - **Lungs**: Uninhibited neutrophil elastase → panacinar emphysema, predominantly in lower lobes.
  - **Liver**: Accumulation of A1AT in hepatocytes → hepatitis, cirrhosis, and increased HCC risk.

Clinical Features:

- **Pulmonary**: Panacinar emphysema, progressive dyspnea.
- **Hepatic**: Hepatitis, cirrhosis (15% of cases), risk of hepatocellular carcinoma.

Investigations:

- **Serum**: Low A1AT levels.
- **Electrophoresis**: Decreased alpha-1 peak.
- **Imaging**:
  - **CXR**: Hyperinflation, flat diaphragm, basilar emphysema.
  - **CT**: Panacinar emphysema, bronchiectasis, bullae.
- **Liver Biopsy**: PAS-positive inclusions in hepatocytes, cirrhosis signs.

Management:

- **Lifestyle**: Avoid smoking to prevent accelerated lung damage.
- **Supportive Care**:
  - Vaccinations (e.g., influenza, pneumococcus).
  - Symptomatic relief with bronchodilators.
  - Pulmonary rehabilitation.
- **Medical**: IV A1AT protein concentrates.
- **Surgical Options**:
  - Lung volume reduction.
  - Lung and liver transplantation for end-stage disease.

Key Point: AAT deficiency should be considered in patients presenting with emphysema before age 50.

Acute respiratory distress syndrome (ARDS)

Definition: Acute respiratory failure with hypoxemia and bilateral pulmonary infiltrates, not explained by heart failure or fluid overload.

Causes:

- **Most common**: Sepsis
- Trauma, shock, massive transfusion (TRALI), acute pancreatitis, certain medications (e.g., bleomycin), and primary lung damage (e.g., pneumonia, aspiration).

Pathophysiology:

- Damage leads to inflammatory mediator release → neutrophil migration and damage to alveolar-capillary membrane → alveolar edema, formation of hyaline membranes, impaired gas exchange, and eventual fibrosis.

Phases:

1. **Exudative phase**: Fluid accumulation and non-cardiogenic pulmonary edema.
2. **Hyaline membrane formation**: Decreased surfactant and gas exchange.
3. **Organizing phase**: Type II pneumocyte proliferation and fibrosis.

Clinical Features:

- **Symptoms**: Acute dyspnea, fever, cough, chest pain.
- **Signs**: Tachypnea, cyanosis, diffuse crackles.
- **ABG**: Increased arterial-alveolar oxygen gradient, low compliance, restrictive lung disease.

Diagnostic Criteria (Berlin Criteria):

1. Acute onset within one week of known trigger.
2. Bilateral opacities on imaging.
3. $PaO_2/FiO_2 \leq 300$ mm Hg with PEEP ≥ 5 cm H_2O:
   - Mild: PaO_2/FiO_2 = 201–300 mm Hg.
   - Moderate: PaO_2/FiO_2 = 101–200 mm Hg.
   - Severe: $PaO_2/FiO_2 \leq 100$ mm Hg.
4. Exclusion of heart failure/fluid overload.

Management:

- **ICU Admission**.
- **Oxygenation**:
  - Noninvasive ventilation for mild cases.
  - Intubation for severe or deteriorating cases.
  - **Lung-protective ventilation**:

  - Low tidal volume (6 mL/kg of ideal body weight).
  - PEEP > 5 cm H2O.
  - Maintain SpO2 at 88–95%, PaO2 at 55–80 mm Hg.
- **PEEP**:
  - Increases alveolar recruitment, prevents collapse, and counters hypoxemia.
- **Avoid oxygen toxicity**: Limit FiO2 to <40% when possible.
- **Treat underlying cause.**
- **Advanced treatment**: ECMO for refractory cases.
- **Ineffective treatments**: Diuretics, glucocorticoids (in acute phase).

Key Ventilation Strategies:

- **Low tidal volume ventilation (LTVV)**: Reduces mortality, targets 6 mL/kg of ideal body weight.
- **High PEEP**: Enhances oxygenation and prevents alveolar collapse.

Prognosis:

- High mortality, particularly in severe cases. Early intervention and optimal ventilator settings improve outcomes.

ARDS is associated with:
- Increased arterial-alveolar oxygen gradient.
- Increased elastic recoil.
- **Low pulmonary artery wedge pressure.**
- **Low compliance.**
- **Restrictive lung disease**

Acute respiratory distress syndrome (ARDS) diagnostic criteria:
- **Abnormal x-ray,**
- **Respiratory failure < 1 week after a known or suspected trigger,**
- **Decreased PaO2/FiO2,**
- **Should exclude CHF or fluid overload as a potential cause of respiratory distress.**

The two main ventilator methods used in the management of ARDS are:

- **High positive end-expiratory pressure (PEEP)**
- **Low tidal volume ventilation (LTVV)**

Bronchiectasis

Definition: Permanent airway dilation due to chronic infection or inflammation.

Causes:

- **Post-infective**: Tuberculosis, pneumonia, whooping cough.
- **Secretion clearance disorders**: Cystic fibrosis, primary ciliary dyskinesia, ABPA, Kartagener syndrome.
- **Immunodeficiency**: Common variable immunodeficiency, HIV.
- **Chronic inflammatory diseases**: Rheumatoid arthritis, Sjogren syndrome.
- **Other**: Lung cancer, smoking, α1-antitrypsin deficiency, yellow nail syndrome.

Clinical Features:

- Chronic productive cough with copious sputum.
- Dyspnea, recurrent infections, hemoptysis.
- Crackles and wheeze on examination.
- Fatigue and post-nasal drip.

Diagnosis:

- **Chest X-ray**: Initial test, may show thickened bronchi, "tram-track" lines, ring shadows.
- **HRCT (Gold Standard)**: Reveals tram-track lines, signet ring sign (dilated bronchus larger than adjacent artery).

Subtypes:

- **Cylindrical**: Uniform caliber, tram-track sign (47%).
- **Varicose**: Beaded appearance (9.9%).
- **Cystic**: Cyst-like bronchi, severe with air-fluid levels (45.1%).

Management:

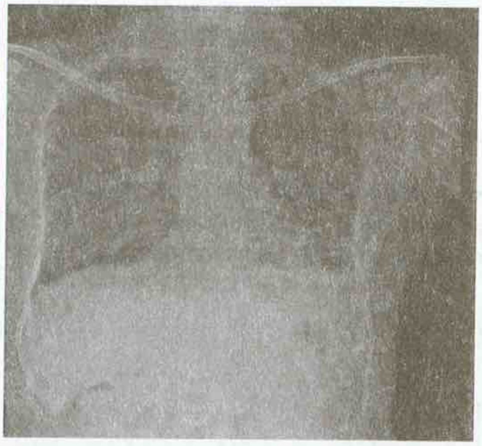
- **Symptom control**: Inspiratory muscle training, postural drainage.
- **Antibiotics**: For exacerbations and long-term rotating use if severe.
- **Vaccinations**: Influenza and pneumococcal.
- **Surgery**: For localized, non-responsive cases.

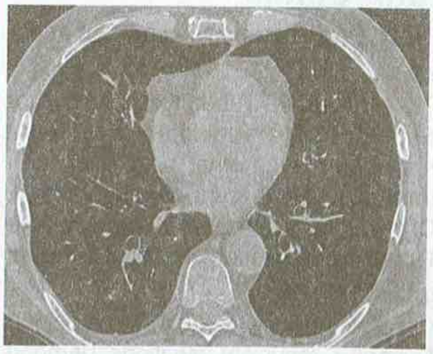
Common Pathogens:

- Haemophilus influenzae (most common).
- Pseudomonas aeruginosa, Klebsiella spp., Streptococcus pneumoniae.

Prevention:

- **Primary**: Antibiotic control of infections in at-risk individuals.
- **Secondary**: Long-term low-dose macrolide treatment for frequent exacerbations.


Chest x-ray showing tramlines, most prominent in the left lower zone


CT chest showing widespread tram-track and signet ring sign

Bronchiectasis: most common organism → *Haemophilus influenzae*

Symptom control in non-CF bronchiectasis → inspiratory muscle training + postural drainage

The mainstay of therapy for bronchiectasis is antibiotics and chest physiotherapy.

Cystic fibrosis

Genetics and Pathophysiology

- **Autosomal recessive disorder** caused by a defect in the **CFTR gene** on chromosome 7 (commonly ΔF508 mutation).
- Leads to abnormal chloride transport → thick, sticky secretions affecting lungs, pancreas, liver, and reproductive system.
- **Inheritance**: 25% chance of being affected if both parents are carriers.

Epidemiology

- **Incidence**: 1 in 2,500 live births; more common in Caucasians, rare in Afro-Caribbean and Asian populations.
- **Carrier frequency**: 1 in 25 in white populations.
- **Late diagnosis**: 10% diagnosed in adulthood.

Clinical Features

- **Growth and Puberty**: Failure to thrive, delayed puberty.
- **Infertility**:
  - **Males**: 98% due to congenital bilateral absence of the vas deferens.
  - **Females**: Subfertility due to thick cervical mucus.

- **Pancreatic Insufficiency**:
    - Present in 85% of adult patients; can cause diabetes and malabsorption.
- **Respiratory Issues**:
    - Recurrent chest infections, ABPA (15% of adults), pneumothorax.
- **Other**:
    - **Liver disease** (30% by adulthood), nasal polyps, GI complications like distal intestinal obstruction syndrome, renal calculi.

Diagnosis

- **Sweat Chloride Test**:
    - **≥60 mmol/L**: Confirms CF.
    - **30-59 mmol/L**: Intermediate; repeat testing needed.
- **Genetic Testing**: Confirms CFTR mutations.
- **False results**: Various metabolic and genetic disorders may affect sweat chloride results.

Management

- **Pulmonary Care**:
    - **Airway clearance**: Chest physiotherapy, mucolytics (rhDNase, hypertonic saline).
    - **Medications**: Anti-inflammatories, Lumacaftor-Ivacaftor for ΔF508 mutation.
- **Nutritional Support**:
    - High-calorie diet, vitamin supplementation, pancreatic enzyme replacement.
- **Lung Transplant**: Considered for severe cases with criteria such as FEV1 <30%.
- **Infections**:
    - **Common pathogens**: S. aureus (children), P. aeruginosa (adults), Burkholderia cepacia (poor prognosis).
    - **Antibiotic Regimens**: Tailored for acute and chronic infections.

Complications

- **Chronic Respiratory Failure, pulmonary hypertension**, and **liver disease**.
- **Prognosis**:
    - Median survival now at least 40 years for children born in the 1990s.

Children whose parents are both heterozygous carriers of cystic fibrosis have a 25% chance of being affected by the condition.

Distal intestinal obstruction syndrome is the most common bowel complication in cystic fibrosis after **Gastroesophageal reflux disease (GERD)**

In cystic fibrosis, *Staphylococcus aureus* infections are more common in childhood while *Pseudomonas* infections become more common in late adolescence and adulthood.

Occupational lung diseases

Occupational asthma

Definition: Occupational asthma is a type of asthma triggered by exposure to specific substances in the workplace, characterized by airway inflammation, bronchospasm, and reversible airflow limitation.

Causes:
- **Sensitizers**: Substances that induce an allergic response over time (e.g., flour, animal dander, latex, isocyanates).
- **Irritants**: Substances causing non-allergic asthma (e.g., chlorine, smoke, ammonia).

Risk Factors:
- Specific occupations: Bakers, healthcare workers, chemical industry workers, animal handlers, and hairdressers.
- Pre-existing asthma or atopy.

Types:
- **Allergic Occupational Asthma**: Develops after sensitization period; IgE-mediated response.
- **Irritant-Induced Asthma** (Reactive Airways Dysfunction Syndrome - RADS): Acute onset after high-level exposure to irritants.

Clinical Features:
- Cough, wheezing, chest tightness, and shortness of breath.
- Symptoms often improve on weekends or vacations and worsen during work periods.

Diagnosis:
- **Detailed Occupational History**: Essential to identify exposure-related patterns.
- **Peak Expiratory Flow (PEF) Monitoring**: Shows variability correlating with work and non-work periods.
- **Spirometry**: May show reversible airflow obstruction.
- **Allergy Testing**: Helps identify specific sensitizers.
- **Methacholine Challenge Test**: Can assess airway hyperresponsiveness.

Management:
- **Avoidance of Exposure**: Primary intervention to prevent disease progression.
- **Pharmacological Treatment**:
  - **Inhaled Corticosteroids (ICS)** and **Bronchodilators** for symptom control.
- **Workplace Modifications**: Engineering controls, use of PPE, and changing job duties.
- **Relocation**: May be necessary if exposure avoidance is not feasible.

Occupational asthma should be suspected in all adult patients with asthma.

Isocyanates are the most common cause of occupational asthma

Serial peak flow measurements at work and at home are used to detect occupational asthma

Hypersensitivity pneumonitis (HP) (also called extrinsic allergic alveolitis)

Definition: Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an inflammatory lung disease caused by repeated inhalation of organic antigens, leading to immune-mediated lung inflammation.

Causes:

- **Common Exposures**:
  - **Farmer's Lung**: Moldy hay, straw (Thermophilic actinomycetes).
  - **Bird Fancier's Lung**: Bird droppings, feathers.
  - **Humidifier Lung**: Contaminated humidifiers or air conditioners.
  - **Other**: Moldy wood, grain dust, and certain chemicals in industry.

Types:

- **Acute HP**: Rapid onset after exposure, with flu-like symptoms (fever, cough, dyspnea).
- **Subacute HP**: Gradual onset with chronic cough and dyspnea.
- **Chronic HP**: Long-term exposure leads to irreversible lung damage and fibrosis.

Symptoms:

- Cough, shortness of breath, and fatigue.
- Acute form may include fever, chills, and malaise after exposure.

Diagnosis:

- **History of Exposure**: Essential for identifying potential causes.
- **Chest X-ray/CT**: Ground-glass opacities, fibrosis in chronic cases.
- **Pulmonary Function Tests (PFTs)**: Typically restrictive pattern.
- **Serology**: Detection of specific antibodies against suspected antigens.

Management:

- **Avoidance of Antigen Exposure**: Key to prevent disease progression.
- **Corticosteroids**: For acute symptoms or significant inflammation.
- **Pulmonary Rehabilitation**: For chronic cases with lung damage.

Saccharopolyspora rectivirgula causes farmer's lung, a type of EAA

Aspergillus clavatus causes malt workers' lung, a type of EAA

A recurrent common cold with an irritating cough and fever may indicate hypersensitivity pneumonitis.

Disease	Antigen Source
Farmer's lung (**The commonest occupational hypersensitivity pneumonitis)**	**spores of Saccharopolyspora rectivirgula** (commonly from **Contaminated hay**)
Bird fanciers' lung	avian proteins
Malt workers' lung	*Aspergillus clavatus*
Mushroom workers' lung	thermophilic actinomycetes
Maple bark stripper's lung	Cryptostroma corticale
Cheese washer's lung	Penicillium casei

Pneumoconiosis

Definition: Pneumoconiosis is a group of occupational lung diseases caused by inhalation of mineral dusts that leads to lung inflammation and fibrosis.

Types and Causes:

- **Coal Workers' Pneumoconiosis (CWP)**: Inhalation of coal dust.
- **Silicosis**: Caused by silica dust from mining, quarrying, and construction.
- **Asbestosis**: Caused by asbestos fibers, common in construction and shipbuilding.
- **Berylliosis**: From beryllium exposure, seen in electronics and aerospace industries.

Clinical Features:

- Chronic cough, shortness of breath, and fatigue.
- Symptoms vary by type, with some specific signs:
  - **CWP**: Black sputum (melanoptysis).
  - **Silicosis**: Increased risk of tuberculosis.
  - **Asbestosis**: Pleural plaques and high risk of mesothelioma.
  - **Berylliosis**: Granulomatous inflammation.

Diagnosis:

- **Chest X-ray/CT**: Shows characteristic findings for each type (e.g., nodules in silicosis, pleural plaques in asbestosis).
- **Pulmonary Function Tests (PFTs)**: Often show restrictive patterns.

Management:

- **Prevent Further Exposure**: Key to management.
- **Symptomatic Relief**: Includes bronchodilators, pulmonary rehabilitation, and, if necessary, oxygen therapy.
- **Regular Monitoring**: To check for complications, including lung cancer and infections.

Exposure to isocyanates most likely associated with squamous-cell carcinoma of the bronchus.

Asbestosis

Definition: Asbestosis is a chronic lung disease caused by inhaling asbestos fibers, leading to progressive lung fibrosis.

Risk Factors: Common in construction, shipbuilding, insulation, and industries using asbestos-containing materials.

Symptoms:

- Gradual onset of shortness of breath, especially with exertion
- Persistent dry cough
- Chest pain in advanced stages
- Clubbing of fingers in severe cases

Diagnosis:

- **Chest X-ray/CT**: Shows diffuse interstitial fibrosis, predominantly in the lower lobes, and may show pleural plaques (a hallmark of asbestos exposure).
- **Pulmonary Function Tests (PFTs)**: Typically show a restrictive pattern with reduced lung volumes.

Complications:

- **Lung Cancer**: Significantly increased risk, especially with smoking.
- **Mesothelioma**: A rare, aggressive cancer of the pleura uniquely associated with asbestos exposure.
- **Pleural Plaques**: Benign but indicate asbestos exposure.

Management:

- **Avoid Further Exposure**: Essential to slow progression.
- **Symptom Management**: Oxygen therapy for hypoxia, pulmonary rehabilitation.
- **Monitoring**: Regular check-ups to detect complications like lung cancer or mesothelioma

> **The most common malignancy associated with asbestosis is bronchogenic carcinoma, not mesothelioma**

Pleural mesothelioma

Definition

- Malignant tumor of mesothelial cells of pleura

Epidemiology

- More common in male than female (3:1)

Risk factors

- Asbestos (20- to 40-year after exposure)
- **Smoking**, alcohol, and diet **do not** increase the risk.
- **Loss of material from chromosome 22 is commonly seen in mesothelioma cell lines**

Features

- History of asbestos exposure in 85-90%, latent period of 20-40 years
- Dyspnoea, weight loss, chest wall pain
- pleural effusion

Diagnosis

- Chest x-ray showing either a pleural effusion or pleural thickening
- **CT chest with contrast → the best next step after chest x-ray**
  - ⇨ Multiple nodular pleural lesions (pleural thickening)
- **Pleurocentesis** (If a pleural effusion is present) for biochemistry and cytology
  - ⇨ exudative and hemorrhagic pleural fluid.
  - ⇨ **cytology is only helpful in 20-30% of cases**
  - ⇨ don't rely on cytology alone to confirm the diagnosis
- **Thoracoscopy biopsy**
  - ⇨ **the most important investigation to confirm the diagnosis.**
  - ⇨ used to investigate cytology negative exudative effusions as it has a high diagnostic yield (around 95%).
  - ⇨ Psammoma bodies are seen on histology
- Positron emission tomography (PET) with CT (PET-CT) as the initial **staging** after histopathological confirmation of the diagnosis.

Management

- Radiation, with or without chemotherapy
- Surgery (pleurectomy or pneumonectomy) in severe cases if operable

Prognosis

- Poor. The median survival after diagnosis is 1- 2 years
- **Bronchogenic carcinoma** is the most common malignant pulmonary tumor in patients with asbestosis

Silicosis

Definition: Silicosis is a lung disease caused by inhaling silica dust, leading to inflammation and fibrosis.

Risk Factors: Common in occupations involving mining, quarrying, construction, and glass manufacturing.

Types:

- **Chronic Silicosis**: Develops over decades with prolonged low-level exposure.
- **Accelerated Silicosis**: Occurs within 5-10 years of high exposure.
- **Acute Silicosis**: Develops within weeks to years of intense exposure; rapid and severe.

Symptoms:

- Persistent cough
- Shortness of breath
- Fatigue
- Increased susceptibility to infections, especially tuberculosis

Diagnosis:

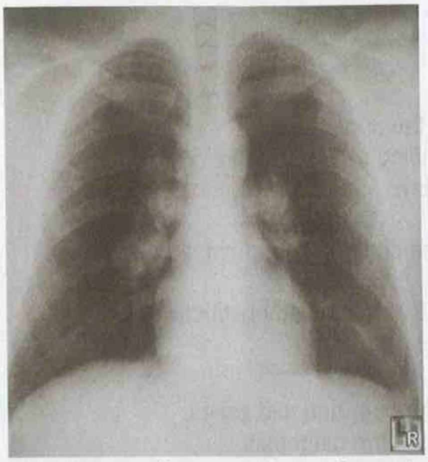
- **Chest X-ray/CT**: Shows "egg-shell" calcifications in lymph nodes and nodular fibrosis, primarily in the upper lobes.
- **Lung Function Tests**: Often show a restrictive pattern in advanced stages.

Management:

- **Exposure Prevention**: Key to stopping disease progression.
- **Symptomatic Treatment**: Bronchodilators, pulmonary rehabilitation.
- **Monitoring**: Regular screening for tuberculosis.

Complications

- ↑ **susceptibility to TB (silica is toxic to macrophages)**
- ↑ incidence of primary **lung cancer**
- ↑ risk of connective-tissue disease, vasculitis, (COPD), and chronic renal failure.



The chest radiograph shows **"eggshell" calcification** of the hilar lymph nodes, as seen with **silicosis.**

Berylliosis

Definition: Berylliosis, or chronic beryllium disease (CBD), is a lung condition caused by inhaling beryllium dust or fumes, leading to a granulomatous inflammatory response.

Risk Factors: Commonly affects workers in aerospace, nuclear, electronics, and manufacturing industries where beryllium exposure occurs.

Symptoms:

- Persistent dry cough
- Shortness of breath
- Fatigue, weight loss
- Joint pain

Diagnosis:

- **Chest X-ray/CT**: Shows nodules, often in the upper lobes, and signs of fibrosis.
- **Beryllium Lymphocyte Proliferation Test (BeLPT)**: Confirms sensitivity to beryllium.
- **Lung Biopsy**: Shows noncaseating granulomas similar to those in sarcoidosis.

Management:

- **Avoid Exposure**: Essential to prevent disease progression.
- **Corticosteroids**: Primary treatment to reduce inflammation.
- **Immunosuppressive Therapy**: Used in severe cases.

Coal workers' pneumoconiosis (CWP)

Pathology

- Results from inhaling and depositing coal dust particles in the lungs.
- **Carbon-Laden Macrophages**: "Dust cells" filled with carbon accumulate, primarily affecting the upper lobes.

Types

- **Simple CWP**:
  - Centrilobular emphysema-like changes.
  - Small, fine nodular opacifications (<1 cm) in the upper lungs.
  - Often asymptomatic, usually an incidental finding on chest X-ray.
- **Complicated CWP (Progressive Massive Fibrosis)**:
  - Associated with high silicon dust exposure.
  - Nodular opacities (1-2 cm) with larger masses on imaging (>1 cm, sometimes up to 10 cm).
  - "Sausage-shaped" mass characteristic on CT with a mixed obstructive and restrictive pattern on PFT.

Diagnosis

- **Chest X-Ray**: Shows small interstitial nodules in the upper and mid zones.
- **Histologic Hallmark**: Carbon-laden macrophages confirm diagnosis.

Complications

- Increased risk of **connective-tissue disease** and **COPD**.
- **Caplan Syndrome**: CWP associated with rheumatoid arthritis.
- No significant association with lung cancer or tuberculosis.

Management

- **Prevention**: Workplace dust control, PPE, and regular health screenings.
- **Symptom Management**: **Bronchodilators** for airflow issues, **oxygen therapy** for severe cases.
- **Pulmonary rehabilitation** for improved function.
- **Address Complications**: Treat associated COPD, Caplan syndrome, and manage melanoptysis.
- **Regular Monitoring**: Ongoing imaging and lung function tests to track progression.
- **Advanced Case**: Lung transplant for severe, end-stage cases.

Caplan's syndrome

- **Coal workers pneumoconiosis associated with rheumatoid arthritis**
- **Typically bilateral, peripheral nodules 5 mm to 5 cm in size**
- **peripheral lung nodules with the histopathology of rheumatoid nodules develop on a background of pneumoconiotic opacities.**
- **In contrast to pneumoconiotic masses, they can develop rapidly, over a period of weeks, and may cavitate or calcify.**

The presence of carbon-laden macrophages is the histologic hallmark of coal workers' pneumoconiosis.

Coughing up of black sputum (melanoptysis) is pathognomonic of coal workers pneumoconiosis.

Although coal is mined from under the earth, the upper lobes of the lungs are primarily affected.

Primary Ciliary Dyskinesia (PCD)

Definition

A rare genetic disorder causing dysfunctional cilia and impaired mucociliary clearance.

Key Features

- **Recurrent Respiratory Infections**: Can lead to bronchiectasis.
- **ENT Issues**: Chronic sinusitis, otitis media, and conductive hearing loss.
- **Infertility**: Affects sperm motility in males; increases ectopic pregnancy risk in females.
- **Kartagener's Syndrome**: Situs inversus with sinusitis and bronchiectasis in 50% of cases.

Diagnosis

- **Screening**: Low nasal nitric oxide (NNO) levels.
- **Confirmation**: Ciliary analysis with videomicroscopy or electron microscopy; genetic testing for dynein mutations.

Treatment

- **Infection Control**: Nebulized hypertonic saline and maintenance azithromycin.

Kartagener's syndrome

Definition

Kartagener's Syndrome is a rare, inherited disorder characterized by a triad of:

1. **Primary Ciliary Dyskinesia (PCD)**: Defective cilia movement leading to poor mucus clearance.
2. **Situs Inversus**: Reversal of major visceral organs (e.g., heart on the right side).
3. **Chronic Sinopulmonary Infections**: Due to impaired mucus clearance.

Genetics

- **Inheritance**: Autosomal recessive.
- **Cause**: Mutations affecting cilia structure, often in genes like **DNAI1** or **DNAH5**.

Pathophysiology

- Defective ciliary function causes impaired mucus transport in respiratory and reproductive tracts.
- Leads to chronic respiratory infections and bronchiectasis.
- **Situs Inversus**: Occurs due to disrupted ciliary function during embryonic development, affecting organ positioning.

Clinical Features

- **Respiratory**:
  - Chronic cough, recurrent sinusitis, nasal polyps.

  - Chronic bronchitis, bronchiectasis, and recurrent pneumonia.
- **ENT**: Chronic rhinosinusitis, middle ear infections.
- **Reproductive**:
  - Male infertility (due to immotile sperm).
  - Female subfertility or infertility (due to impaired fallopian tube cilia).
- **Situs Inversus**: Detected incidentally on imaging or physical exam.

Diagnosis

1. **Imaging**:
   - **Chest X-ray/CT Scan**: Shows situs inversus, bronchiectasis.
2. **Nasal Nitric Oxide Test**: Low levels suggest PCD.
3. **Electron Microscopy of Cilia**: Shows structural abnormalities in cilia.
4. **Genetic Testing**: Confirms mutations in genes related to ciliary function.

Management

- **Airway Clearance**: Physiotherapy, mucolytics, bronchodilators.
- **Antibiotics**: For managing and preventing respiratory infections.
- **Surgery**: May include sinus surgery or lung transplant in severe cases.
- **Reproductive Counseling**: Given fertility challenges.

Prognosis

- **Chronic Disease**: Management improves quality of life but requires lifelong care.
- **Complications**: Bronchiectasis, hearing loss, and recurrent infections can impact life expectancy and quality.

primary ciliary dyskinesia (PCD) + situs inversus → Kartagener's syndrome

Kartagener syndrome: triad of:

1. **situs inversus,**
2. **chronic sinusitis, and**
3. **bronchiectasis.**

Lung cancer

Classification of Lung Cancer

Type	Subtype	Description
Non-Small Cell Lung Cancer (NSCLC)	Adenocarcinoma	Most common, especially in non-smokers; peripheral lung location.
	Squamous Cell Carcinoma	Strong association with smoking; usually central lung location.
	Large Cell Carcinoma	Rare, undifferentiated; can be central or peripheral.
Small Cell Lung Cancer (SCLC)	-	Highly aggressive with rapid growth and early metastasis; strongly linked to smoking.

Epidemiology

- Second most common cancer (after breast cancer in women and prostate cancer in men).
- More common in males except for adenocarcinoma, which is more common in women

Risk Factors

- **Smoking**: The primary risk factor, particularly for SCLC and squamous cell carcinoma.
- **Environmental Exposures**: Asbestos, radon, air pollution.
- **Genetic Factors**: Family history and specific genetic mutations (e.g., EGFR, ALK in NSCLC).

Clinical Features

- **Local Symptoms**: Persistent cough, hemoptysis, chest pain, dyspnea.
- **Systemic Symptoms**: Weight loss, fatigue, fever.
- **Paraneoplastic Syndromes**: Especially in SCLC; can include SIADH, Cushing's syndrome, and Lambert-Eaton myasthenic syndrome.

Diagnosis

- **Imaging**:
  - **Chest X-ray** and **CT scan**: Initial studies to identify mass location and size.
  - **PET scan**: For detailed staging, particularly in NSCLC.
- **Bronchoscopy**: Visualizes central tumors and allows for biopsy.
- **Histological Analysis**: Essential for classification and guiding treatment.
- **Staging**:
  - **NSCLC**: TNM staging system (Tumor, Node, Metastasis).
  - **SCLC**: Classified as limited (confined to one hemithorax) or extensive disease.

Lung Cancer: Stepwise Investigations (NICE guiedline)

Investigation	Details
Chest X-ray	- Initial assessment for individuals with symptoms of lung cancer.
Contrast-enhanced CT Scan	- Performed for suspected or known lung cancer to assess the chest, liver, adrenals, and lower neck for diagnosis and staging.
PET-CT	- Recommended for patients eligible for curative treatment to evaluate intrathoracic lymph nodes and detect distant metastases.
Tissue Biopsy	- **Peripheral lesions:** Image-guided biopsy. - **Central lesions:** Flexible bronchoscopy if nodal staging does not affect treatment. - **Mediastinal nodes:** EBUS-TBNA or EUS-FNA if nodal status influences treatment.
MRI	- Used to evaluate the extent of disease in superior sulcus tumours.
Brain Imaging	- Contrast-enhanced brain CT or MRI for patients with stage II or III NSCLC undergoing treatment with curative intent.

Management

Cancer Type	Treatment Options
NSCLC	- **Early-stage**: Surgery (lobectomy or pneumonectomy) - **Advanced-stage**: Chemotherapy, radiotherapy, targeted therapy (e.g., EGFR or ALK inhibitors in specific mutations)
SCLC	- Primarily treated with chemotherapy and radiotherapy - Surgery rarely performed due to early spread

Contraindications to lung cancer surgery include SVC obstruction, FEV < 1.5, MALIGNANT pleural effusion, and vocal cord paralysis

Prognosis

- **NSCLC**: Prognosis varies with stage; early detection improves survival rates significantly.
- **SCLC**: Poor prognosis due to aggressive nature; 5-year survival is under 5% for extensive disease.

Non-small cell lung cancer (NSCLC): adenocarcinoma VS squamous cell carcinoma

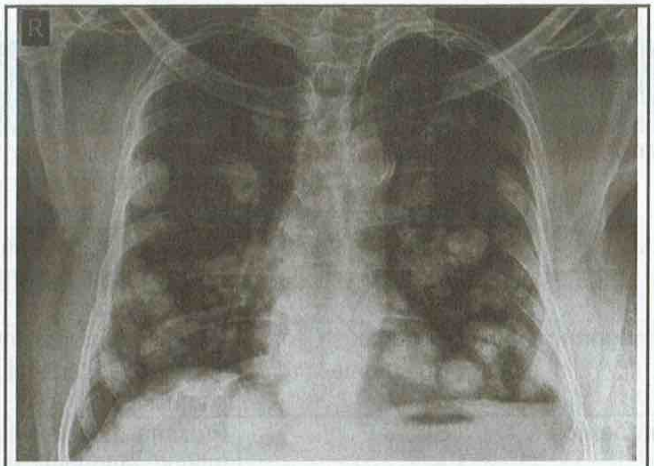
	Lung adenocarcinoma (AC)	Lung squamous cell carcinoma (SCC)
Location	Peripheral	Central
Characteristics	🕮 **Most common type** of lung cancer worldwide 🕮 **More common in women and nonsmokers** 🕮 Prognosis is usually better than in other types of lung cancer	🕮 **Strong association with smoking** 🕮 **Cavitary lesions** arising from a hilar bronchus
Paraneoplastic features	🕮 **Adenocarcinoma: HPOA → Clubbing**	🕮 **PTHrp →Hypercalcemia**
Histology	🕮 Glandular tumor 🕮 Mucin-producing cells (positive mucin staining)	🕮 Solid, epithelial tumor 🕮 Intercellular bridges (desmosomes) 🕮 Keratin pearls

Paraneoplastic features

Paraneoplastic Syndrome	Associated Lung Cancer Type	Clinical Features
Syndrome of Inappropriate ADH Secretion (SIADH)	Primarily Small Cell Lung Cancer (SCLC)	Hyponatremia, low serum osmolality, confusion, seizures
Cushing's Syndrome	SCLC	Hypercortisolism: weight gain, hypertension, hyperglycemia, muscle weakness
Hypercalcemia of Malignancy	Squamous Cell Carcinoma	Increased calcium levels: nausea, vomiting, abdominal pain, confusion
Lambert-Eaton Myasthenic Syndrome (LEMS)	SCLC	Proximal muscle weakness, fatigue, autonomic dysfunction (e.g., dry mouth, erectile dysfunction)
Hypertrophic Pulmonary Osteoarthropathy (HPOA)	NSCLC and occasionally SCLC	Painful periostitis, clubbing of fingers and toes
Dermatomyositis/Polymyositis	NSCLC and SCLC	Muscle weakness, skin rash (heliotrope rash, Gottron's papules)
Acanthosis Nigricans	NSCLC and SCLC	Darkened, velvety skin patches, typically in body folds
Hematologic Abnormalities	NSCLC and SCLC	Anemia, thrombocytosis, leukocytosis, eosinophilia
Neurological Syndromes	SCLC	Encephalomyelitis, peripheral neuropathy, cerebellar degeneration

Paraneoplastic features of lung cancer

- **Squamous cell:** PTHrp →**Hypercalcemia**
- **Adenocarcinoma:** HPOA → Clubbing
- **Small cell:**
  - ⇨ ↑ADH → **SIADH** → **hyponatraemia**
  - ⇨ ↑ACTH → **Cushing syndrome**
  - ⇨ Lambert-Eaton syndrome



Metastatic carcinoma (the most common malignant tumour found in the lung)

Chest X-ray shows secondary tumors as **multiple, well-circumscribed, noncalcified nodules.**

Squamous cell and Small cell lung cancer are both Sentrally (Centrally) located.

Lung adenocarcinoma

- most common type in non-smokers
- peripheral lesion

Coal dust is not a risk factor of lung cancer

Metastatic carcinoma is the most common malignant tumour found in the lung

Carcinoid Lung Tumour

Aspect	Details
Definition	- Neuroendocrine tumours (NETs) of enterochromaffin cell origin. - Originate from Kulchitsky (K) cells in the lung.
Epidemiology	- Accounts for 1% of lung tumours. - 20–30% of all NETs. - Common in individuals aged 40–50 years. - Equal incidence in men and women.
Risk Factors	- Smoking is NOT a risk factor.
Features	- Often asymptomatic. - Recurrent cough and haemoptysis. - Recurrent infections due to bronchial obstruction. - Rarely presents with carcinoid syndrome (bronchospasm, diarrhoea, flushing, right-sided valvular lesions).
Paraneoplastic Syndromes	- ACTH secretion → Cushing's syndrome. - GHRH secretion → acromegaly. - Associated with MEN type 1.
Investigations	- **Chest X-ray:** May show collapse due to distal obstruction. - **Bronchoscopy:** Identifies 80% of tumours; appears as 'cherry-red' vascular lesions; rigid bronchoscopy needed for biopsy due to risk of bleeding. - **Histology:** Compact nests of epithelial cells surrounded by connective tissue. - **Plasma chromogranin A:** Sensitive but not specific. - **24-hour urinary 5-HIAA:** More specific but has false positives/negatives.
Management	- Surgical resection is the primary treatment. - Histology may not be required if clinical presentation is typical.
Prognosis	- 90% 5-year survival if no metastases.

The 'cherry-red' lesion is a typical finding of lung carcinoid.

Lung fibrosis

Definition

- Lung fibrosis, or pulmonary fibrosis, is a chronic, progressive lung disease characterized by scarring (fibrosis) of lung tissue, leading to stiffening and reduced lung function.

Pathophysiology

- **Fibrosis** occurs in the interstitial lung tissue, resulting in thickened alveolar walls, decreased gas exchange, and impaired lung elasticity.
- **Causes**: Abnormal wound healing and inflammation lead to excess deposition of extracellular matrix and collagen.

Causes

- **Idiopathic Pulmonary Fibrosis (IPF)**: Most common, with unknown cause.
- **Occupational and Environmental Exposures**: Asbestos, silica, certain organic dusts.
- **Connective Tissue Diseases**: Rheumatoid arthritis, systemic sclerosis.
- **Medications and Radiation**: Amiodarone, methotrexate, radiation therapy.
- **Genetics**: Familial forms linked to specific genetic mutations.

Clinical Features

- **Symptoms**: Progressive dyspnea (shortness of breath), dry cough, fatigue.
- **Physical Exam**: Bibasilar "Velcro" crackles, clubbing of fingers in advanced cases.

Diagnosis

- **High-Resolution CT (HRCT)**: Shows honeycombing, ground-glass opacities, and reticular markings.
- **Pulmonary Function Tests (PFTs)**: Restrictive pattern with reduced total lung capacity (TLC) and diffusing capacity (DLCO).
- **Lung Biopsy**: May be required if diagnosis is unclear.

Management

- **Medications**: Antifibrotic agents like pirfenidone and nintedanib slow disease progression in IPF.
- **Supportive Therapy**: Oxygen therapy, pulmonary rehabilitation.
- **Lung Transplant**: Considered for advanced cases in eligible patients.

Prognosis

- **Progressive Disease**: Limited treatment options; survival typically 3-5 years from diagnosis in IPF.
- **Complications**: Respiratory failure, pulmonary hypertension

Causes of Lung Fibrosis by Predominantly Affected Zones

Predominantly Upper Zone Fibrosis	Predominantly Lower Zone Fibrosis
Occupational Exposures - Coal worker's pneumoconiosis - Silicosis	**Idiopathic Pulmonary Fibrosis (IPF)**
Hypersensitivity Pneumonitis (especially chronic)	**Connective Tissue Diseases** - Rheumatoid arthritis - Systemic sclerosis
Granulomatous Diseases - Sarcoidosis - Ankylosing spondylitis	**Asbestos Exposure** (Asbestosis)
Infections - Tuberculosis (fibrosis after healed infection) - Fungal infections (e.g., histoplasmosis)	**Drug-Induced Fibrosis** - Amiodarone, methotrexate, nitrofurantoin
Medications - Certain chemotherapeutic agents (e.g., bleomycin)	**Other Causes** - Cryptogenic Organizing Pneumonia (COP) - Idiopathic interstitial pneumonia (non-IPF types)

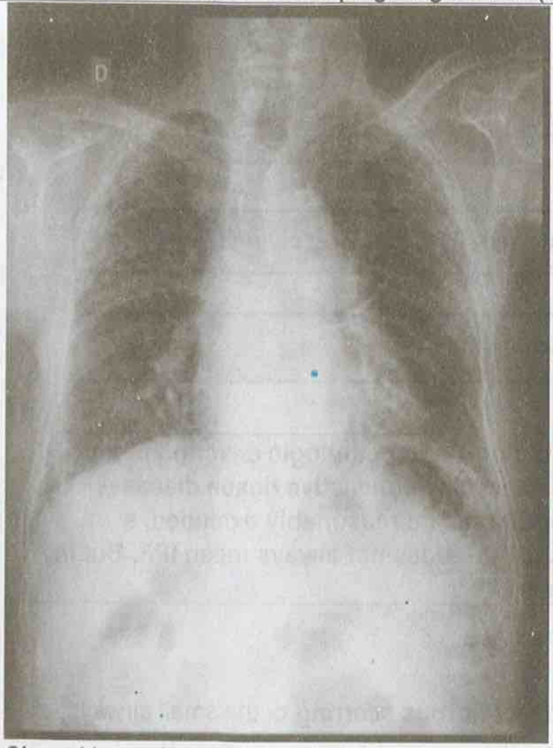
Management

- **Supportive care** (e.g., supplemental oxygen, pulmonary rehabilitation, seasonal influenza and pneumococcal vaccination)
- **Antifibrotic agents → pirfenidone or nintedanib**
  - ⇨ **Action** → suppresses fibroblast proliferation
  - ⇨ **Indication** → mild-moderate disease IPF (FVC 50-80 % predicted).
  - ⇨ **Benefit** → reduces disease progression by 30 %
  - ⇨ **Side effects** → drug-induced liver injury

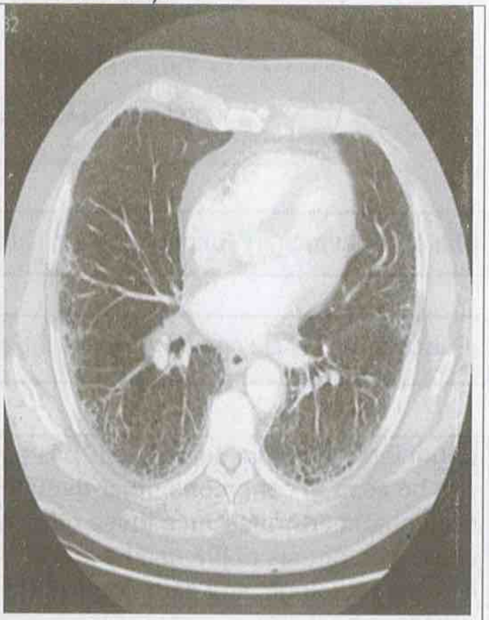
- **Immunosuppressants** such as azathioprine, prednisolone, and mycophenolate mofetil **should not be used** in IPF.
- **Lung transplant**

Prognosis

- poor, average life expectancy is around 3-4 years
- increased risk of developing lung cancer (by 7- to 14-fold).



Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs.



CT scan showing advanced pulmonary fibrosis, including 'honeycombing.'

Usual interstitial pneumonia (UIP) is a radiologic and pathologic description that can be seen in conditions other than IPF, especially connective tissue diseases and rheumatoid arthritis. Once these other conditions are reasonably excluded, a clinical diagnosis of IPF can be made. Hence, UIP does not always mean IPF. However, in IPF, the radiologic and pathologic pattern is UIP.

Acronym for causes of upper zone fibrosis: CHARTS

- **C- Coal worker's pneumoconiosis**
- **H - Histiocytosis/ hypersensitivity pneumonitis**
- **A - Ankylosing spondylitis**
- **R - Radiation**
- **T - Tuberculosis**
- **S - Silicosis/sarcoidosis**

Baseline pulmonary function testing is important in patients receiving bleomycin

Pulmonary fibrosis can occur following pneumonia

Usual interstitial pneumonia (UIP): is a radiologic and pathologic description and can be seen in conditions other than IPF, especially connective tissue diseases, rheumatoid arthritis. Once these other conditions are reasonably excluded, a clinical diagnosis of IPF can be made. Hence UIP does not always mean IPF. But in IPF, the radiologic and pathologic pattern is UIP.

Bronchiolitis obliterans (BO)

Definition: Bronchiolitis obliterans is the term for **fibrous scarring** of the small airways, characterised by **fixed airway obstruction**.

Mechanism

- submucosal and peribronchiolar inflammation and fibrosis **without any intraluminal granulation tissue**
- BO should not be confused with bronchiolitis obliterans organising pneumonia (BOOP), a completely different disease.

Causes

- Inhalation of toxic fumes
- Exposure to mineral dust
- Respiratory infections: Viral, Mycoplasma, Legionella
- post-transplantation: Bone marrow, heart-lung or lung transplantation
- Connective tissue disorder: **Rheumatoid arthritis** or **SLE**
- **Penicillamine treatment**
- Inflammatory bowel disease

Feature: dry cough and dyspnoea. Wheeze might be audible.

Diagnosis

- Should be considered in a nonsmoker when airflow limitation is irreversible or associated with a gas transfer abnormality.
- Should be considered in association with recent toxic fume exposure, symptoms of viral infection, history of organ transplantation, or concomitant rheumatic disease.
- **HRCT**: shows expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules
- **Spirometry** → mixed obstructive/restrictive picture
- **Transfer factor may be low but the transfer coefficient (Kco) is often normal.**
- **lung biopsy**
  - ⇨ An open or thoracoscopic lung biopsy is required to make a definitive diagnosis
  - ⇨ will show→ a mural concentric narrowing of the lumina of the bronchioles.
  - ⇨ Transbronchial lung biopsy is often **inadequate** for diagnosis because the disease is patchy.

Differential Diagnosis

Condition	BO Key Differences
Asthma	BO shows **irreversible** airflow obstruction, whereas asthma is **reversible** on spirometry.
COPD	COPD is typically associated with a significant **smoking history** and lacks the exposure to etiologic agents specific to BO.
Cryptogenic Organising Pneumonia (COP)	COP presents with **restrictive** lung pattern on spirometry and **granulation tissue** in alveoli and bronchioles; responds well to corticosteroids, unlike BO.

Treatment

- No optimal treatment. Patients rarely respond to steroids and the prognosis is poor.
- This disease is irreversible and severe cases often require a lung transplant

Obstructive sleep apnoea (OSA)

Definition

- OSA is characterized by the cessation of breathing during sleep due to upper airway obstruction, leading to episodes of apnea (≥10 seconds of respiratory arrest) and hypopnea (≥50% reduction in airflow for ≥10 seconds).

Epidemiology

- More common in men (2:1 male-to-female ratio).

Causes

- **Primary risk factor**: Obesity
- Other factors: Macroglossia (acromegaly, hypothyroidism, amyloidosis), large tonsils, Marfan's syndrome, small pharyngeal opening, COPD, sedative use (alcohol), neck size >43 cm (17 inches).

Clinical Features

- **Daytime symptoms**: Excessive sleepiness, morning headaches
- **Nighttime symptoms**: Loud snoring, gasping, choking, breathing interruptions
- **Associated Signs**: Repetitive apneas and hypopneas during sleep

Complications

- Pulmonary hypertension, cor pulmonale
- Cardiac arrhythmias, risk of sudden death, myocardial infarction, and stroke

- Increased accident risk due to microsleep episodes
- Metabolic syndrome (hypertension, insulin resistance), neurocognitive impairment
- Polycythemia due to hypoxia-induced erythropoietin secretion

Diagnosis

- **Sleep Studies**:
  - **Overnight polysomnography (gold standard)**
  - Diagnosis criteria based on Apnea-Hypopnea Index (AHI):
    - **≥15 episodes/hour** or **≥5 episodes/hour** with symptoms (e.g., daytime sleepiness, cognitive dysfunction) or comorbidities (e.g., hypertension).
  - **Severity based on AHI**:
    - Mild: 5-14 episodes/hour
    - Moderate: 15-30 episodes/hour
    - Severe: >30 episodes/hour

Management

- **First-Line**: Weight loss for definitive control, CPAP (Continuous Positive Airway Pressure) for moderate/severe cases
- **Alternative Options**:
  - **Oral appliances** (e.g., mandibular advancement) if CPAP is not tolerated or for mild OSA
  - **Upper airway surgery** if CPAP or oral devices are ineffective or declined
- **Additional Measures**: Avoid sedatives/alcohol, consider Modafinil for daytime sleepiness in CPAP-treated cases

Obstructive sleep apnea is the most common causes of secondary hypertension.

The diagnosis of obstructive sleep apnea requires sleep studies and should not be made based on clinical tools or questionnaires alone such as Epworth Sleepiness Scale (used to diagnose excessive daytime sleepiness) or Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

In-laboratory polysomnography is the gold standard for the diagnosis of sleep-related breathing disorders

Following weight loss, CPAP is the first-line treatment for moderate/severe obstructive sleep apnoea

Obesity hypoventilation syndrome (OHS) (Pickwick syndrome)

Definition

- a combination of obesity (body mass index [BMI] ≥30 kg/m^2) and daytime hypercapnia ($PaCO_2$ ≥45 mm Hg in arterial blood gas analysis) in the absence of other causes for hypoventilation.

Diagnostic criteria

- BMI ≥ 30 kg/m^2 .Commonly affects **morbidly obese individuals**. 90% of patients with OHS have coexistent OSA.
- Arterial blood gasses showing diurnal hypercapnia ($PaCO_2$ > 45 mm Hg)
  ⇨ serum bicarbonate ≥ 27 mEq/L
- Polysomnography: hypoventilation during sleep with or without obstructive apnea events
- Exclusion of other possible causes of hypoventilation (eg, neuromuscular disease).

Treatment

- 1st line: noninvasive positive airway pressure (PAP) together with lifestyle modifications for weight loss.

> **Obesity + feature of OSA + diurnal abnormal ABG (↑ PCO2) → (OHS)**

Pneumothorax

Definition

- Pneumothorax is the presence of air within the pleural space, leading to partial or complete lung collapse.

Types and Causes

Type	Description	Causes
Primary Spontaneous Pneumothorax (PSP)	Occurs without an apparent cause and in the absence of lung disease	- Often in tall, thin young males - Associated with smoking and family history
Secondary Spontaneous Pneumothorax (SSP)	Occurs in patients with underlying lung disease	- COPD, asthma, cystic fibrosis - Interstitial lung disease, lung cancer, infections
Traumatic Pneumothorax	Caused by penetrating or blunt trauma to the chest	- Rib fractures, stab wounds, gunshot wounds - Iatrogenic causes (e.g., central line insertion, mechanical ventilation)
Tension Pneumothorax	A life-threatening variant with trapped air under pressure compressing the lung and mediastinum	- Can arise from any type of pneumothorax - Often due to trauma or positive-pressure ventilation

Clinical Features

- **General Symptoms**: Sudden onset of sharp chest pain, dyspnea.
- **Physical Exam**:
  - Decreased or absent breath sounds on the affected side
  - Hyper-resonance to percussion
  - Decreased chest wall movement on the affected side
- **Tension Pneumothorax**: Tracheal deviation away from the affected side, hypotension, distended neck veins, and cyanosis (medical emergency).

Investigations

- **Chest x ray:** 1st step to **confirm the diagnosis**
  - ⇨ Questions sometimes discuss the size of the pneumothorax in percentage terms rather than giving the interpleural distance.
    - A **30%** pneumothorax ≈ **2 cm**
    - A 50% pneumothorax is likely to have a rim of > 3cm.
- **CT chest**
  - ⇨ **The next step after chest x-ray to investigate the underlying cause of recurrent pneumothorax**
- **Video assisted thoracoscopy**
  - ⇨ If CT not help in pointing to **underlying cause of recurrent pneumothorax**

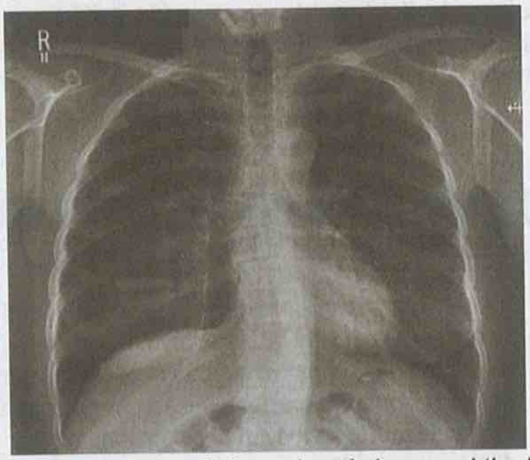
Management

Type	Definition	Management
Primary Pneumothorax	- Age <50 years, minimal/no smoking history, no underlying lung disease. - Caused by rupture of apical pleural blebs.	- **Rim of air <2 cm, not breathless:** Consider discharge. - **Rim of air ≥2 cm or breathless:** Perform needle aspiration. - **After aspiration (rim <2 cm, improved breathing):** Consider discharge with outpatient follow-up. - **Aspiration fails (>2 cm or breathless):** Insert chest drain. - Administer oxygen at 10 L/min if required.
Secondary Pneumothorax	- Age ≥50 years or significant smoking history or underlying lung disease.	- **Rim of air <2 cm:** Perform aspiration. - **Rim of air ≥2 cm:** Insert small-bore chest drain (8–14 FG) with underwater seal. - **Aspiration fails (>1 cm):** Insert chest drain. - **Severely dyspnoeic (even if <2 cm):** Insert chest drain. - Admit all patients for at least 24 hours. - Administer high-flow oxygen to aid pleural air reabsorption.

Type	Definition	Management
Tension Pneumothorax	- Sudden deterioration in patients on mechanical or nasal non-invasive ventilation; often missed in ICU.	- **Suspected tension pneumothorax:** Perform needle thoracocentesis with 3–6 cm cannula. - Leave cannula in place until bubbling is confirmed in the underwater-seal system.

Complications

- **Recurrence**: High risk, particularly in PSP and SSP.
- **Persistent Air Leak**: May require surgery or pleurodesis.
- **Tension Pneumothorax**: Can cause cardiac arrest if not promptly treated.



Chest x ray reveals a 3.2 cm rim of air around the lung.

Pleural effusion

Definition

- Pleural effusion is an abnormal accumulation of fluid in the pleural space.

Classification, Pathophysiology, and Causes

Type	Pathophysiology	Light's Criteria	Causes
Exudate	Increased capillary permeability (e.g., inflammation)	- Pleural fluid protein/serum protein ratio > 0.5 - Pleural fluid LDH/serum LDH ratio > 0.6 - Pleural fluid LDH > ⅔ upper limit of normal serum LDH	- Infection (e.g., pneumonia, TB) - Connective tissue disease (e.g., RA, SLE) - Neoplasia (e.g., lung cancer) - Pancreatitis - Pulmonary embolism - Dressler's syndrome

Type	Pathophysiology	Light's Criteria	Causes
Transudate	Increased capillary hydrostatic pressure or decreased oncotic pressure	- Pleural fluid protein/serum protein ratio ≤ 0.5 - Pleural fluid LDH/serum LDH ratio ≤ 0.6 - Pleural fluid LDH < ⅔ upper limit of normal serum LDH	- Heart failure - Hypoalbuminemia (e.g., liver disease, nephrotic syndrome) - Hypothyroidism - Meigs' syndrome

Clinical Features

- **Small effusion (<300 mL)**: Often asymptomatic.
- **Larger effusion (>300 mL)**: Tachypnea, pleuritic chest pain, cough, and symptoms of underlying disease (e.g., fever in infection, cachexia in malignancy).
- **Other findings**: Ascites suggests hepatic hydrothorax or Meigs syndrome; unilateral lower extremity swelling suggests DVT with PE; lymphadenopathy may indicate malignancy.

Investigations

Test	Purpose
Chest X-ray	Initial imaging to detect pleural fluid.
Ultrasound	Detects fluid and guides pleural aspiration.
Pleural Aspiration	Fluid analysis for pH, protein, LDH, cytology, and microbiology.
CT Chest	For suspected pleural or parenchymal pathology.
Thoracoscopy/VATS	Used if cytology-negative exudative effusions remain undiagnosed.
Blood Tests	Assess NT-proBNP for heart failure, liver enzymes, serum TSH, and albumin levels to identify underlying conditions.

Pleural Infection and Drainage Indications

- **Indications for Chest Tube Insertion**:
  - Frankly purulent fluid
  - Pleural pH < 7.2
  - Positive Gram stain
  - Loculated effusions
  - Poor clinical response to antibiotics

Characteristic Pleural Fluid Findings

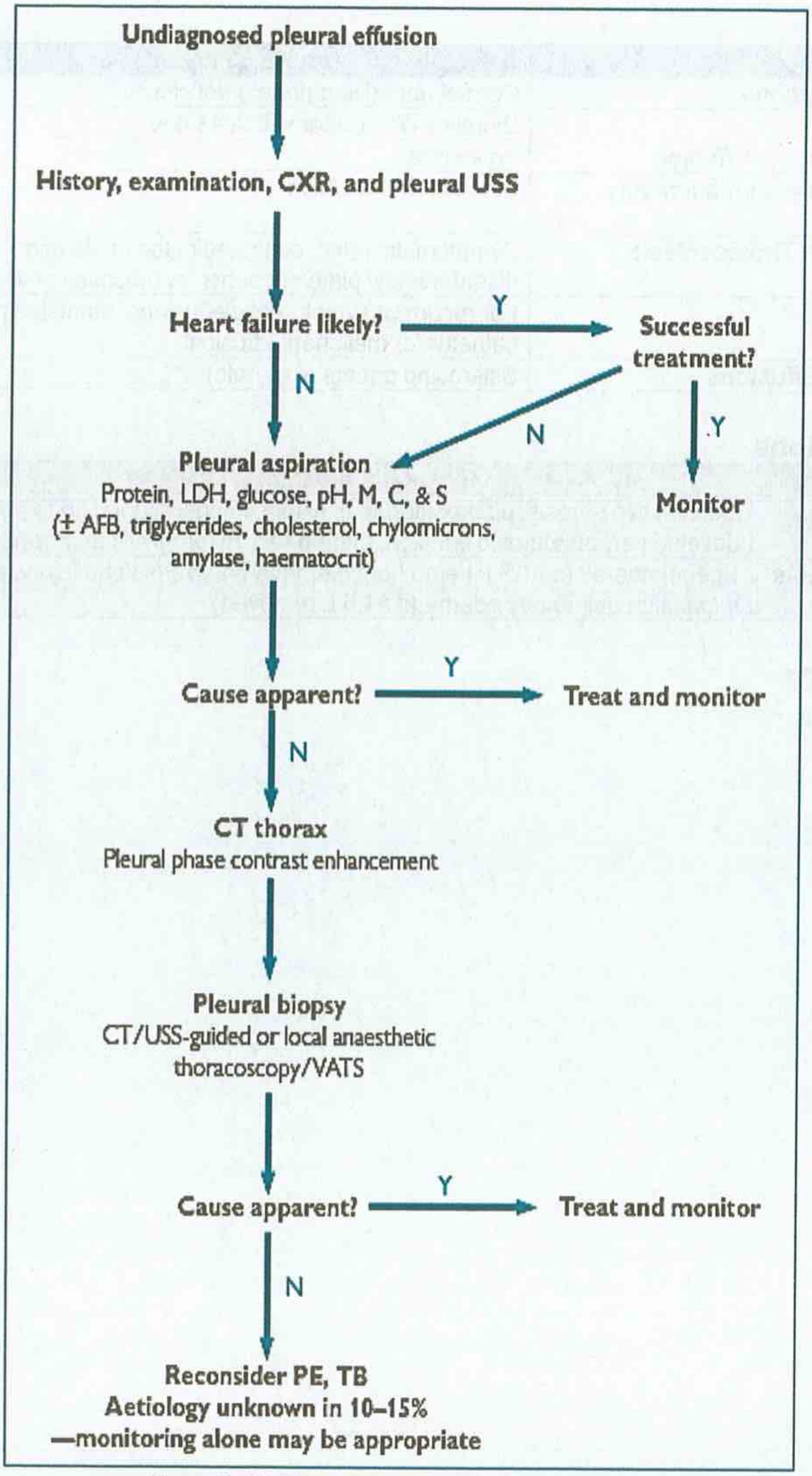
Finding	Associated Conditions
Low Glucose	Empyema, rheumatoid arthritis, tuberculosis, malignancy
Raised Amylase	Pancreatitis, esophageal perforation
Heavy Blood-Staining	Malignancy, mesothelioma, pulmonary embolism, tuberculosis

Treatment

Condition	Management
Hypoproteinemia	Correct underlying protein deficiency.
CHF	Diuretics (75% clear within 48 hours).
Parapneumonic Effusion	Antibiotics
Rheumatologic/Inflammatory Conditions	Steroids and NSAIDs
Therapeutic Thoracentesis	Symptomatic relief, contraindicated in bleeding disorders, low platelet counts, or mechanical ventilation
Pleurodesis	For recurrent symptomatic effusions; tunnelled pleural catheter for malignant effusions
Malignant Effusions	Sclerosing agents (e.g., talc)

Complications

Procedure	Complications
Pleural Effusion	Constrictive fibrosis, pleurocutaneous fistula; in pneumonia, up to 40% develop parapneumonic effusion, and up to 10% progress to empyema
Thoracentesis	Pneumothorax (5-10%), hemothorax, empyema, liver/spleen injury, re-expansion pulmonary edema (if >1.5 L removed)



Diagnostic algorithm for the patient with a pleural effusion

Oxford handbook of respiratory medicine. 3rd edition

Meigs syndrome: A triad of ascites, right pleural effusion, and benign ovarian tumor

Exudate typically appears cloudy, has an increased cell count, and has high levels of protein, albumin, and LDH.

Transudate is usually clear, has a decreased cell count, and has low levels of protein, albumin, and LDH.

MEAT has low glucose: **M**alignancy, **E**mpyema, **A**rthritis (rheumatoid pleurisy), and **T**uberculosis are causes of pulmonary effusion associated with low glucose levels.

Pleural fluid with a bloody appearance suggests a malignant etiology or haemothorax

Hypereosinophilic Syndrome

Definition

- Hypereosinophilic Syndrome (HES) is a rare, chronic disorder characterized by persistent and marked eosinophilia (eosinophil count >1500 cells/µL for more than six months) associated with eosinophil-mediated damage to multiple organs.

Etiology and Types

- **Primary (Myeloproliferative HES)**: Due to mutations in hematopoietic stem cells, such as the *FIP1L1-PDGFRA* fusion gene.
- **Secondary (Reactive HES)**: Due to an underlying cause such as infections, autoimmune disorders, or cancers.
- **Idiopathic HES**: No identifiable cause.

Pathophysiology

- Excessive eosinophils infiltrate various organs, leading to inflammation, tissue damage, and organ dysfunction.
- Commonly affected organs include the skin, heart, lungs, gastrointestinal tract, and nervous system.

Clinical Features

Organ/System	Symptoms
Skin	Rash, itching, angioedema, erythematous plaques
Heart	Endomyocardial fibrosis, heart failure, thromboembolism
Lungs	Cough, dyspnea, pulmonary infiltrates
Gastrointestinal	Abdominal pain, nausea, vomiting, diarrhea
Nervous System	Peripheral neuropathy, headache, confusion, cognitive dysfunction

Diagnosis

- **Blood Tests**: Persistent eosinophilia (>1500 cells/µL).
- **Bone Marrow Biopsy**: To assess for myeloproliferative variants and cytogenetic abnormalities (e.g., *FIP1L1-PDGFRA* mutation).

- **Imaging**: Chest X-ray, echocardiogram, and abdominal ultrasound to evaluate organ involvement.
- **Exclusion of Secondary Causes**: Rule out infections, autoimmune disorders, and malignancies.

Management

- **First-Line**: Corticosteroids are the mainstay for reducing eosinophil counts and preventing organ damage.
- **Targeted Therapies**:
  - **Tyrosine Kinase Inhibitors**: Imatinib for *FIP1L1-PDGFRA* mutation-positive HES.
  - **Monoclonal Antibodies**: Mepolizumab, an anti-IL-5 antibody, for steroid-refractory cases.
- **Cytotoxic Drugs**: Hydroxyurea for cases requiring additional eosinophil reduction.

Eosinophilic Pneumonia

Definition

- Eosinophilic pneumonia is a group of lung diseases characterized by eosinophil accumulation in the lungs and blood, leading to inflammation and respiratory symptoms.

Types

1. **Acute Eosinophilic Pneumonia (AEP)**: Rapid onset, often linked to environmental exposures or infections.
2. **Chronic Eosinophilic Pneumonia (CEP)**: Gradual onset, commonly associated with asthma or allergic conditions.

Etiology

- Often idiopathic.
- Associated with infections (especially parasitic), medications, environmental exposures, or autoimmune diseases.
- CEP is commonly related to underlying allergic or atopic conditions.

Clinical Features

Type	Symptoms
AEP	Rapid onset of fever, cough, dyspnea, hypoxemia; patients may present with acute respiratory failure
CEP	Gradual onset with chronic dry cough, wheezing, dyspnea, weight loss, and fatigue; often seen in asthmatic patients

Diagnostic Features

- **Blood Tests**: Elevated eosinophil count in peripheral blood (may be high in both AEP and CEP).
- **Imaging**: Bilateral infiltrates on chest X-ray or CT.
  - CEP often shows characteristic peripheral infiltrates, described as "photographic negative of pulmonary edema."
- **Bronchoalveolar Lavage (BAL)**: Shows high eosinophil percentage, confirming diagnosis.
- **Lung Biopsy**: Occasionally needed for definitive diagnosis if other causes cannot be excluded.

Management

- **Acute Eosinophilic Pneumonia**: Responds well to corticosteroids; treatment usually short-term.
- **Chronic Eosinophilic Pneumonia**: Long-term corticosteroids often required to prevent relapses.

Prognosis

- **AEP**: Excellent with prompt treatment, often resolving fully.
- **CEP**: Good with treatment, but relapses are common, requiring prolonged or repeated courses of corticosteroids.

The classic presentation of idiopathic acute eosinophilic pneumonia is the rapid onset of acute respiratory failure in a previously healthy patient. diffuse radiographic opacities, and bronchoalveolar lavage with ≥25 % eosinophils, and absence of infection or other known precipitant.

Tropical Pulmonary Eosinophilia (TPE) vs. Löffler's Syndrome

Feature	Tropical Pulmonary Eosinophilia (TPE)	Löffler's Syndrome
Definition	Hypersensitivity reaction to filarial parasites, primarily *Wuchereria bancrofti* and *Brugia malayi*	Transient pulmonary reaction caused by migration of parasites (e.g., *Ascaris lumbricoides*)
Epidemiology	Endemic in tropical and subtropical regions, especially Southeast Asia, India, and Africa	Found worldwide, often related to areas with high parasite exposure
Etiology	Immune reaction to microfilariae trapped in the lung capillaries	Migration of helminth larvae through lungs (e.g., *Ascaris*, *Strongyloides*)
Pathophysiology	Immune-mediated destruction of microfilariae in pulmonary capillaries causes eosinophilic inflammation	Transient eosinophilic response to parasite passage through lungs
Clinical Features	- Persistent cough - Wheezing - Dyspnea, especially at night - Fever and weight loss	- Mild cough - Wheezing - Mild dyspnea and chest pain - Self-limiting symptoms
Pulmonary Symptoms	Chronic and severe, can be debilitating	Mild and transient, resolves within days to weeks
Extra-pulmonary Symptoms	Fever, malaise, weight loss	Typically absent
Blood Eosinophilia	Marked eosinophilia (>3000 cells/μL)	Moderate eosinophilia (often <1000 cells/μL)
Imaging	Chest X-ray shows reticulonodular infiltrates and diffuse lung involvement	Chest X-ray may show transient, migratory pulmonary infiltrates
Diagnosis	- Elevated IgE levels - Positive filarial serology - High blood eosinophils	- Blood eosinophilia - History of parasite exposure - Chest X-ray

Feature	Tropical Pulmonary Eosinophilia (TPE)	Löffler's Syndrome
Treatment	Diethylcarbamazine (DEC) for 2-3 weeks	Typically self-limiting; treat underlying parasite if identified
Prognosis	Good with treatment, though chronic disease may lead to lung damage if untreated	Excellent; usually resolves without complications

Summary:
- **Tropical Pulmonary Eosinophilia (TPE)** is a severe hypersensitivity reaction due to filarial infections in endemic regions, with persistent and debilitating symptoms and marked eosinophilia, requiring antiparasitic treatment.
- **Löffler's Syndrome** is a transient, mild reaction caused by parasitic migration through the lungs, with self-limiting symptoms and moderate eosinophilia that usually resolves on its own.

The diagnostic criteria for tropical pulmonary eosinophilia include:
1) history of residence or travel to a filarial endemic region,
2) paroxysmal nocturnal cough with dyspnoea,
3) leucocytosis with peripheral blood eosinophilia >3,000/microL,
4) elevated serum IgE and an antifilarial antibodies (IgG and IgE) levels,
5) pulmonary infiltrations in chest x-ray, and
6) clinical improvement with DEC (diethylcarbamazine).

Cryptogenic organising pneumonia (COP)

Definition
- A rare type of inflammatory interstitial lung disease, characterised by a buds of **granulation tissue in the alveoli and bronchioles on histopathology**
- other names: Bronchiolitis obliterans organising pneumonia (BOOP)

Causes
- **Idiopathic:** most common '**cryptogenic** means **unknown cause**'.
- Secondary organising pneumonia: connective tissue disease, malignancy, infection, drugs and toxins

Epidemiology
- Typically, age of onset is 50 to 60 years
- Men and women affected equally.

Feature
- Mimic community-acquired pneumonia (eg, cough, dyspnea with exertion, weight loss).

Investigations
- Chest X-ray: bilateral patchy infiltrates
- Chest CT: multiple ground-glass or consolidative opacities that tend to be at the lung periphery
    - ⇨ **Reversed halo sign**, better known as an atoll sign (a region of ground-glass opacity surrounded by crescentic or annular denser tissue) .
- Pulmonary function tests (PFTs) →restrictive pattern

Diagnosis

- Exclusion of any possible cause (e.g. COVID-19 → do PCR)
- For **definitive diagnosis** → **lung biopsy** → excessive proliferation or **"plugs" of granulation tissue within alveolar ducts and alveoli** (Masson bodies). Granulation tissue extends uniformly into the alveolar ducts and **does not distort pulmonary architecture, unlike usual interstitial pneumonia.**
    - ⇨ If clinical presentation, radiographic appearance and bronchoscopy with bronchoalveolar lavage is consistent with COP, surgical lung biopsy is not required for diagnosis.

Treatment

- **1st line:** Prednisolone (usually effective)
- **2nd line:** cyclophosphamide or azathioprine

Prognosis: Relapse is common

> **Cryptogenic organizing pneumonia (COP)**
>
> - **High-resolution CT of the chest → bilateral ground-glass opacities**
> - **Exclude other possible causes**
> - **Persistent pulmonary opacities despite antibiotic treatment.**
> - **Lung biopsy → granulation tissue plugs in small airways**

Pulmonary hypertension (PH)

Definition

- Pulmonary Hypertension (PH) is defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, as measured by right heart catheterization.
- A pre-capillary component is identified if the pulmonary vascular resistance (PVR) exceeds 2 Wood units.

Classification of PH (Based on Etiology)

Group	Description
Group 1	Pulmonary Arterial Hypertension (PAH) - idiopathic, heritable, drug-induced, associated with conditions (e.g., connective tissue diseases).
Group 2	PH due to Left Heart Disease.
Group 3	PH associated with Lung Diseases and/or Hypoxia (e.g., COPD, sleep apnea).
Group 4	PH due to Chronic Thromboembolic Pulmonary Hypertension (CTEPH).
Group 5	PH with unclear and/or multifactorial mechanisms (e.g., sarcoidosis).

Diagnostic Approach

- **Suspicion**: Based on symptoms such as exertional dyspnea, fatigue, and signs of right heart dysfunction.
- **Detection**: Echocardiography to estimate pulmonary pressures and assess right heart function.
- **Confirmation**: Right heart catheterization for definitive diagnosis and hemodynamic assessment.

Additional Evaluations

- Pulmonary function tests, imaging studies (e.g., chest CT, V/Q scan), and laboratory tests (e.g., autoimmune serologies, HIV) are used to identify underlying causes and classify PH type.

Risk Assessment

- **Risk Stratification**: Essential for treatment guidance, involving clinical assessment, exercise capacity, biomarkers, and hemodynamic measurements.
- **Risk Categories**: Low, intermediate, or high, based on assessments to guide management decisions.

Treatment Strategies

Strategy	Details
General Measures	Supportive therapies, including oxygen supplementation, diuretics for volume overload, and anticoagulation in specific cases.
Pharmacological Therapy for PAH (Group 1)	Combination therapy with agents like endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin analogues. Treatment is tailored based on risk profile and therapy response.
Management of CTEPH (Group 4)	Surgical pulmonary endarterectomy for eligible patients. Medical therapy or balloon pulmonary angioplasty may be considered for inoperable cases or residual PH.
PH Due to Left Heart Disease (Group 2) and Lung Diseases (Group 3)	Focus on treating the underlying heart or lung disease, as specific PH-targeted therapies are not beneficial in these groups.

Follow-Up and Monitoring

- **Regular Monitoring**: Includes clinical evaluation, echocardiography, biomarker assessment (e.g., BNP), and exercise testing (e.g., 6-minute walk test) to monitor disease progression, treatment response, and side effects.

Special Considerations

- **Pregnancy**: PH poses significant maternal risks; effective contraception and pre-pregnancy counseling are recommended for women of childbearing age.
- **Rehabilitation**: Structured exercise and rehabilitation programs may enhance functional capacity and improve quality of life for PH patients.

Sarcoidosis

Definition

- Sarcoidosis is a systemic granulomatous disease of unknown cause, characterized by the formation of non-caseating granulomas in multiple organs, primarily affecting the lungs and lymphatic system.

Clinical Features

System	Features
Respiratory (90%)	Cough, dyspnea, chest pain, pulmonary infiltrates, and fibrosis in advanced cases
Lymphatic	Bilateral hilar lymphadenopathy (BHL)
Skin	Erythema nodosum, lupus pernio (purple skin lesions on face), maculopapular rash

System	Features
Eyes	Uveitis, conjunctivitis, dry eyes
Cardiac	Arrhythmias, heart block, cardiomyopathy
Nervous System	Cranial nerve palsies (especially facial nerve), peripheral neuropathy, meningitis
Musculoskeletal	Arthralgia, arthritis, bone lesions
Liver and Spleen	Hepatosplenomegaly
Hypercalcemia	Granulomas increase production of 1,25-dihydroxyvitamin D, leading to hypercalcemia and hypercalciuria

Sarcoidosis Investigations

Investigation	Details
Chest X-ray	- **Best initial test.** - Abnormal in 85% of cases. - Findings: Bilateral hilar lymphadenopathy, lung fibrosis (upper zones).
CT Scan	- **Next step after chest X-ray in atypical presentations.** - Shows fibrosis, micronodules, fissure nodularity, bronchial distortion, ground-glass shadowing. - May avoid biopsy if diagnostic.
Tissue Biopsy	- **Gold standard test.** - Shows non-caseating granulomas. - Transbronchial lung biopsy is the investigation of choice for confirmation. - Skin biopsy for skin lesions.
Routine Blood Tests	- CBC: Leukopenia in 5–10%. - ESR: Elevated. - Creatinine: Elevated in renal involvement. - Electrolytes: Hypercalcaemia (10%). - Hypergammaglobulinaemia (30–80%).
Exclusion of Other Diseases	- Exclude TB: Sputum/BAL washings for AFB. - Occupational history to rule out berylliosis and silicosis.
Lung Function (Spirometry)	- Restrictive defect with decreased Tlco and Kco.
Cardiac Involvement	- **ECG: May show prolonged PR interval (heart block).** - Abnormal ECG/echocardiogram confirmed with CMR or PET.
CNS Involvement	- CSF: Intrathecal oligoclonal band production, elevated protein, lymphocytosis.
Broncho-alveolar Lavage	- Shows lymphocytosis. - Increased CD4+/CD8+ ratio.
ACE Levels	- Sensitivity 60%, specificity 70%. - **Not reliable for diagnosis but may monitor disease activity.**
Kveim Test	- No longer performed due to cross-infection concerns.

Staging (Pulmonary Sarcoidosis)

Stage	Description
Stage 1	Bilateral hilar lymphadenopathy (BHL) only
Stage 2	BHL with pulmonary infiltrates
Stage 3	Pulmonary infiltrates without BHL
Stage 4	Pulmonary fibrosis

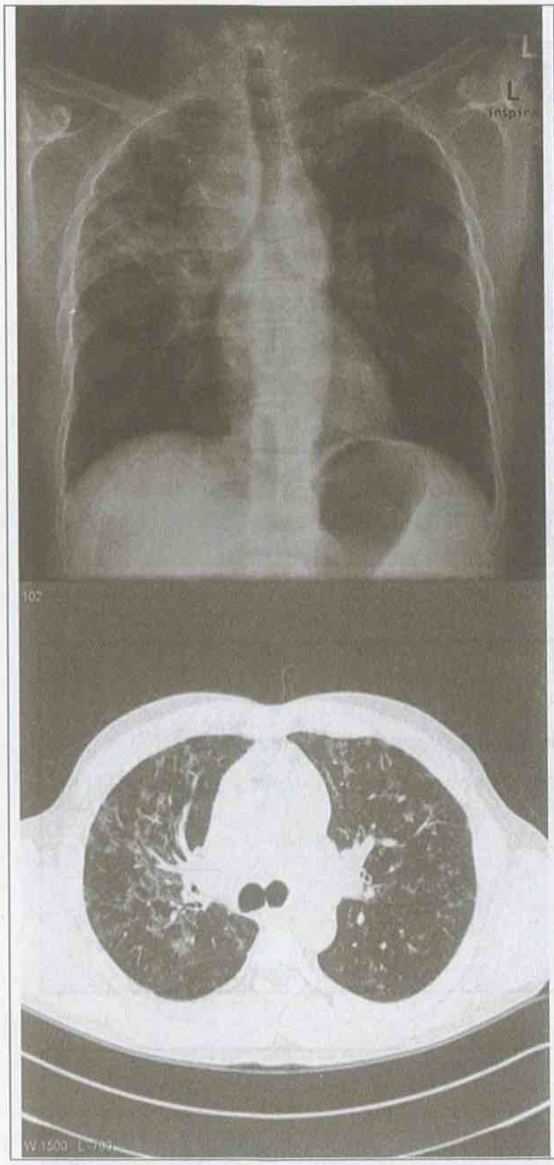
Management

- **Observation**: Many cases resolve spontaneously, particularly in asymptomatic patients.
- **Medications**:
  - First-line: Corticosteroids (prednisolone) for symptomatic disease.
  - **Second-line**: Immunosuppressants (e.g., methotrexate, azathioprine, or hydroxychloroquine) for steroid-refractory or steroid-dependent cases.
- **Calcium Management**: Avoid vitamin D and calcium supplements in patients with hypercalcemia.

Sarcoidosis is a diagnosis of exclusion of granulomatous lung diseases, including tuberculosis and histoplasmosis. Occupational history should be taken to exclude both berylliosis and silicosis which can present in a similar manner to sarcoidosis.

The majority of patients with sarcoidosis get better without treatment

Erythema nodosum is associated with a good prognosis in sarcoidosis.



Chest x-ray and CT scan showing stage 2 sarcoidosis with both bilateral hilar lymphadenopathy + interstitial infiltrates.

The reticulonodular opacities are particularly noted in the upper zones.

Remember that pulmonary fibrosis (which this case has not yet progressed to) may be divided into conditions which predominately affect the upper zones and those which predominately affect the lower zones - sarcoidosis is one of the former.

The CT of the chest demonstrates diffuse areas of nodularity predominantly in a peribronchial distribution with patchy areas of consolidation particularly in the upper lobes.

There is some surrounding ground glass opacities. No gross reticular changes to suggest fibrosis.

Differential Diagnosis

Differential diagnosis of bilateral hilar lymphadenopathy

- Sarcoidosis
- Infections: Tuberculosis, HIV
- Malignancy (lymphoma)
- Cystic fibrosis
- Churg Strauss disease
- Extrinsic allergic alveolitis
- Phenytoin
- Pneumoconiosis, especially **berylliosis** (exposure to beryllium in nuclear power, telecommunications, semi-conductor and electronics industries.)

Variants of sarcoidosis

Lofgren's syndrome

Definition: a variant of sarcoidosis with **acute** clinical presentation with **tetrad of:**

1. **Migratory polyarthritis (acute arthritis), most commonly involves ankles (>90 %).**
2. **Erythema nodosum.**
3. **Bilateral hilar lymphadenopathy.**
4. **Fever.**

Prognosis: Carries an excellent prognosis

Treatment: Usually self-limiting

Heerfordt syndrome

Definition: a variant of sarcoidosis with **chronic** clinical presentation with **tetrad of:**

1. **Parotitis**
2. **Uveitis**
3. **Facial palsy**
4. **Fever**

Yellow nail syndrome

Definition: the triad of

1. **Pulmonary disease** (bronchiectasis, pleural effusions and chronic sinusitis),
2. **Lymphedema:** dysfunction of lymphatic drainage (bilateral lower limbs swelling)
3. **Yellow nails** (thick, opaque and curved)

Cause is unknown

Affects adults over age 50.

Pulmonary Alveolar Microlithiasis (PAM) Summary Table

Aspect	Details
Definition	- Rare hereditary disorder characterised by the accumulation of calcium phosphate microliths in the alveoli.
Aetiology	- Caused by mutations in the **SLC34A2** gene encoding a sodium-dependent phosphate transporter responsible for surfactant recycling in the lung.
Epidemiology	- Rare; typically affects individuals aged 20–40 years. - Often familial with autosomal recessive inheritance.
Clinical Features	- Often asymptomatic in early stages. - Progressive dyspnoea, dry cough, and exercise intolerance. - Late stages: respiratory failure.
Radiological Findings	- **Chest X-ray:** Sand-like micronodules, predominantly in mid and lower lung zones, with a "black pleura" sign (subpleural sparing). - **CT scan:** Diffuse calcifications, septal thickening, and subpleural nodularity.
Diagnosis	- **Confirmed by lung biopsy** showing intra-alveolar microliths. - Genetic testing for **SLC34A2** mutations.
Differential Diagnosis	- Silicosis, pneumoconiosis, metastatic pulmonary calcification, and other interstitial lung diseases with calcification.
Management	- No specific treatment available. - Symptomatic management: oxygen therapy for hypoxaemia, pulmonary rehabilitation. - Lung transplantation for severe cases with respiratory failure.
Prognosis	- Slowly progressive with eventual development of respiratory failure in advanced cases.

Pulmonary Alveolar Proteinosis (PAP)

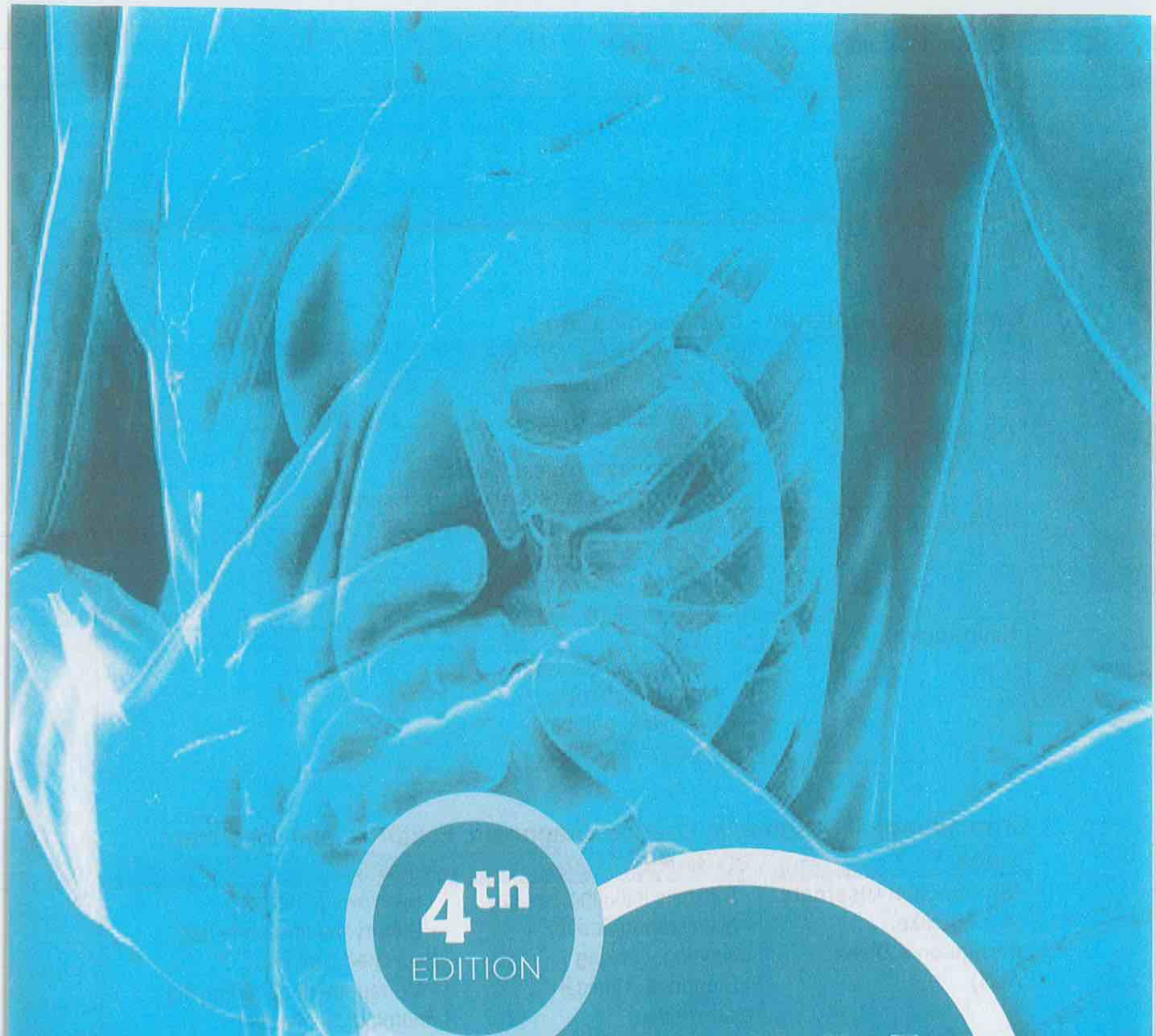
Aspect	Details
Definition	- Rare disorder characterised by the accumulation of lipoproteinaceous material in the alveoli due to impaired surfactant clearance.
Aetiology	- **Primary (Autoimmune):** Caused by autoantibodies against GM-CSF (granulocyte-macrophage colony-stimulating factor). - **Secondary:** Associated with haematological malignancies, inhalation of mineral dusts, or infections. - **Congenital:** Mutations in surfactant-related genes.
Epidemiology	- Most common in adults aged 30–50 years (autoimmune form). - Male predominance.
Clinical Features	- Gradual onset of dyspnoea and dry cough. - Fatigue and hypoxaemia. - Symptoms may range from asymptomatic to severe respiratory failure.
Radiological Findings	- **Chest X-ray:** Bilateral alveolar opacities, typically perihilar ("bat-wing" appearance). - **CT scan:** Crazy paving pattern (interlobular septal thickening with ground-glass opacities).
Diagnosis	- **Bronchoalveolar lavage (BAL):** Milky fluid with surfactant proteins. - **Histopathology:** Periodic acid-Schiff (PAS)-positive material in alveoli. - **Serology:** Anti-GM-CSF antibodies for autoimmune PAP.
Differential Diagnosis	- Pulmonary oedema, organising pneumonia, pneumocystis pneumonia, interstitial lung diseases.
Management	- **Whole lung lavage (WLL):** Standard treatment for autoimmune PAP, involves washing out alveolar material. - **Recombinant GM-CSF therapy:** Used in autoimmune PAP to restore surfactant clearance. - Treat underlying cause in secondary PAP.

Carbon monoxide poisoning

Carbon monoxide (CO) poisoning
Pathophysiology → increased affinity of carbon monoxide with haemoglobin results in tissue hypoxia
The most common symptom is → headache
Standard pulse oximetry (SpO_2) is unable to distinguish between oxyhemoglobin and COHb.
Diagnosis: blood gas analysis to confirm the diagnosis based on the carboxyhaemoglobin (COHb) level. ▪ < 3% → non-smokers ▪ < 10% → smokers ▪ 10 - 30% → symptomatic: headache, vomiting ▪ > 30% → severe toxicity
Treatments: ▪ Mild to moderate →100% high-flow oxygen via a non-rebreather mask ▪ Sever: COHb > 30%, complicated with CNS or cardiac events or pregnancy → hyperbaric oxygen

PassOnExam

THIS PAGE INTENTIONALLY LEFT BLANK



4th EDITION

CHAPTER-5

Gastroenterology

By:

Yousif Abdallah Hamad

Oesophageal diseases

Dysphagia

Causes of dysphagia - by classification

Classification	Examples
Extrinsic	▪ Mediastinal masses ▪ Cervical spondylosis
Oesophageal wall	▪ Achalasia ▪ Diffuse oesophageal spasm ▪ Hypertensive lower oesophageal sphincter
Intrinsic	▪ Tumours ▪ Strictures ▪ Oesophageal web ▪ Schatzki rings
Neurological	▪ CVA ▪ Parkinson s disease ▪ Multiple Sclerosis ▪ Brainstem pathology ▪ Myasthenia Gravis

Oropharyngeal Dysphagia: Causes, Diagnostic Features, and Treatment

Cause	Diagnostic Features	Treatment
Neurological Disorders (e.g., Stroke, Parkinson's Disease, ALS)	- Difficulty initiating swallow - Nasal regurgitation, coughing, choking - Diagnosis: Clinical examination, Videofluoroscopic swallow study (VFSS)	- Swallowing therapy - Dietary modifications (e.g., thickened liquids) - Management of underlying neurological disorder
Muscular Disorders (e.g., Myasthenia Gravis, Muscular Dystrophy)	- Progressive muscle weakness - Fatigue with repetitive swallowing - Diagnosis: Neurological assessment, Electromyography (EMG), VFSS	- Treatment of underlying disorder (e.g., anticholinesterase for Myasthenia Gravis) - Swallowing therapy - Dietary changes
Obstructive Lesions (e.g., Zenker's Diverticulum)	- Progressive difficulty swallowing, regurgitation, sensation of food sticking - Diagnosis: Endoscopy, Barium swallow	- Endoscopic dilation or surgery for diverticula

Cause	Diagnostic Features	Treatment
Cricopharyngeal Dysfunction (e.g., Cricopharyngeal bar)	- Difficulty initiating swallowing, feeling of food stuck in throat - **Diagnosis:** Barium swallow, VFSS, Manometry	- Cricopharyngeal myotomy - Botulinum toxin injection - Swallowing therapy

Esophageal Dysphagia: Causes, Diagnostic Features, and Treatment

Cause	Diagnostic Features	Treatment
Achalasia	- Difficulty with both solids and liquids - Regurgitation of undigested food, chest pain - **Diagnosis**: Manometry (gold standard), Barium swallow, Endoscopy	- Pneumatic dilation - Surgical myotomy (Heller's myotomy) - Botox injection or medication (e.g., nitrates, calcium channel blockers)
Gastroesophageal Reflux Disease (GERD)	- Heartburn, regurgitation, dysphagia predominantly to solids - Symptoms may improve with proton pump inhibitors (PPIs) - **Diagnosis:** Endoscopy, pH monitoring, Barium swallow	- Lifestyle modifications (e.g., diet, weight loss) - PPIs or H2 blockers - Surgical options (e.g., fundoplication) for refractory cases
Eosinophilic Esophagitis	- History of allergic conditions (e.g., asthma, eczema) - Dysphagia to solids, food impaction - **Diagnosis:** Endoscopy with biopsy (eosinophil count), Barium swallow	- Elimination diet - Swallowed corticosteroids (e.g., budesonide) - PPI therapy
Esophageal Motility Disorders (e.g., Diffuse Esophageal Spasm, Scleroderma)	- Intermittent dysphagia to both solids and liquids, chest pain - **Diagnosis:** Manometry, Endoscopy, Barium swallow	- Calcium channel blockers or nitrates for spasms - Prokinetic agents for scleroderma - Management of underlying condition
Obstructive Lesions (e.g., Tumors, Strictures)	- Progressive difficulty swallowing solids, may progress to liquids - Weight loss, regurgitation, sensation of food sticking - **Diagnosis:** Endoscopy, Barium swallow	- Endoscopic dilation for strictures - Surgery for tumors - Palliative care for malignancy

Cause	Diagnostic Features	Treatment
Systemic Conditions (e.g., Diabetes, Connective Tissue Disorders)	- Dysphagia may be part of systemic disease symptoms (e.g., scleroderma) - **Diagnosis:** Clinical evaluation, Manometry, Endoscopy	- Treatment of underlying condition - Symptomatic management of dysphagia - Prokinetic agents if needed

Dysphagia

- **Dysphagia to** both **solids and liquids** → **Achalasia** (motility disorder)
- **Dysphagia to** solids only → **Oesophageal obstruction** (structural disorder e.g. malignancy)

Dysphagia affecting both solids and liquids from the start - think achalasia

The gold standard test for achalasia is oesophageal manometry

Achalasia

Definition

- Achalasia is a rare motility disorder of the oesophagus characterised by the inability of the Lower Oesophageal Sphincter (LOS) to relax properly and impaired peristalsis of the oesophagus, leading to difficulty swallowing (dysphagia), regurgitation of food, and potential oesophageal dilation.

Pathophysiology

- Primary cause unknown: degeneration of Auerbach's plexus ganglia.
- Leads to **contracted Lower Oesophageal Sphincter (LOS)** and **dilated oesophagus** above LOS.

Presentation

- Commonly appears in **middle-aged individuals**, equally in men and women.
- Symptoms develop slowly over years before diagnosis.
- **Dysphagia** for both **liquids and solids** (distinguishes from structural disorders like malignancy).
- **Regurgitation of food** causing heartburn, cough, and sometimes aspiration pneumonia.
- **Vague chest discomfort** from oesophageal spasms.
- **Weight loss** may occur.
- **Complications**: Increased risk of **Oesophageal cancer**.

Investigations

- **Initial test: Barium swallow** (reveals a dilated oesophagus with a 'bird's beak' appearance).
- **Confirmatory test: Manometry** (shows high LOS tone, lack of peristalsis).
- **Upper endoscopy**: To rule out mechanical causes (pseudoachalasia).
- **Chest X-ray (CXR)**: Wide mediastinum and fluid levels.

Treatment

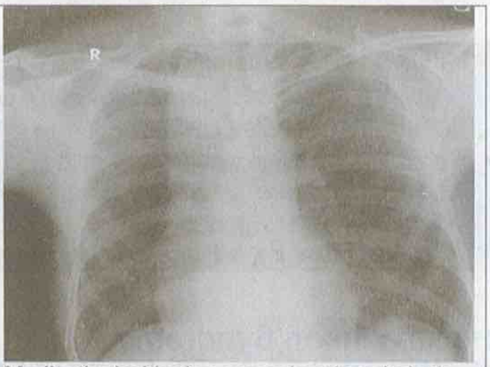
- **First-line (fit patients): Heller cardiomyotomy** (Laparoscopic myotomy).
- **Balloon dilation (Pneumatic dilatation)**: For older/unfit patients (risk of perforation).
- **Botulinum toxin injection**: For patients who can't tolerate dilation or surgery.
- **Drug therapy**: Short-term relief with **isosorbide mononitrate** or **nifedipine** (calcium-channel blocker).

Contraindications

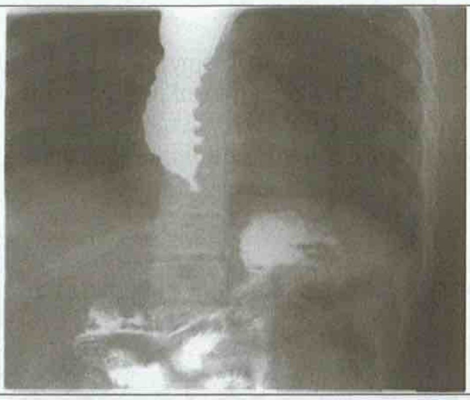
- **Promotility agents (e.g., metoclopramide)** should be avoided as they increase LOS pressure.

Images

classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis



Mediastinal widening secondary to achalasia.

	Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

Differential diagnosis manometry findings:

- Absence of peristalsis in the body of the oesophagus + high lower oesophageal sphincter → **Achalasia**
- Normal contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → **Hypertensive lower oesophageal sphincter**
- High amplitude contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → **Diffuse oesophageal spasm**

Plummer-Vinson Syndrome

Feature	Diagnostic Features
Definition	A rare condition characterized by a triad of dysphagia, iron deficiency anaemia, and oesophagal webs.
Clinical Presentation	- Progressive dysphagia, especially to solids - Fatigue, pallor (from iron deficiency anaemia) - Possible glossitis and angular cheilitis
Laboratory Findings	- Low serum iron and ferritin levels - Microcytic, hypochromic anaemia on blood smear - Rule out other causes of iron deficiency
Imaging and Endoscopy	- Barium swallow: Visualization of esophageal webs - Endoscopy: Direct visualisation and confirmation of webs and rule out malignancy
Treatment	- Iron supplementation (oral or IV) to correct anaemia - Dietary advice to increase iron intake - Esophageal dilation if dysphagia persists despite iron therapy
Complications	- Increased risk of squamous cell carcinoma of the oesophagus - Persistent dysphagia, if not treated properly

Oesophageal Disorders Associated with Severe Vomiting

Aspect	Mallory-Weiss Syndrome	Boerhaave Syndrome
Definition	Longitudinal mucosal tear at the gastro-oesophageal junction or distal oesophagus.	Full-thickness rupture of the oesophagus.
Aetiology	- Sudden increase in intra-abdominal pressure due to severe vomiting or retching. - Alcohol use is a common predisposing factor.	- Sudden increase in intra-oesophageal pressure due to forceful vomiting or retching. - Often occurs in alcoholics or after large meals.
Pathophysiology	Mucosal and submucosal tearing caused by transient pressure gradient between the oesophagus and stomach.	Complete rupture of the oesophageal wall, leading to contamination of the mediastinum with gastric contents.
Clinical Features	- **Acute onset of haematemesis** (bright red blood or "coffee-ground"). - Epigastric or retrosternal pain. - Often follows vomiting or retching.	- **Severe chest pain** (retrosternal or epigastric) radiating to the back. - Vomiting followed by excruciating pain. - Subcutaneous emphysema (crepitus in neck or chest).
Complications	- Bleeding (rarely severe). - Anaemia in chronic cases.	- Mediastinitis. - Sepsis. - Pneumothorax or pleural effusion.
Diagnosis	- **Endoscopy**: Confirms mucosal tear. - **Clinical history**: Vomiting followed by haematemesis.	- **Chest X-ray**: Mediastinal air (pneumomediastinum), subcutaneous emphysema. - **CT Scan**: Oesophageal rupture and mediastinal fluid. - **Contrast Esophagography**: Extravasation of contrast at the rupture site.
Management	- Supportive care: - IV fluids and antiemetics. - Endoscopic haemostasis for active bleeding. - Avoid NSAIDs or aspirin.	- Emergency management: - IV fluids, broad-spectrum antibiotics, and nil by mouth. - Surgery for repair of oesophageal rupture. - Drainage of mediastinal or pleural contamination if needed.
Prognosis	- Excellent with conservative management. - Most cases resolve spontaneously.	- Poor without early diagnosis and treatment. - High mortality if mediastinitis develops.

Key Differences:

- **Mallory-Weiss Syndrome** involves a partial-thickness mucosal tear and presents with **haematemesis**, while **Boerhaave Syndrome** is a full-thickness oesophageal rupture with severe **chest pain** and systemic complications like mediastinitis.
- **Mallory-Weiss** is managed conservatively, whereas **Boerhaave Syndrome** requires **emergency intervention**, often surgical.

Oesophageal web

Oesophageal web	
What is it?	a thin mucosal membrane projecting into the lumen → oesophageal constriction
Common age and gender?	middle-aged females
Common symptoms?	dysphagia and regurgitation of food
Common location?	▪ in the cervical oesophagus near cricopharyngeus muscle. ▪ Typically arise from the anterior wall and never from the posterior wall.
Associations?	1. Plummer-Vinson syndrome 2. graft-versus-host disease 3. gastroesophageal reflux disease 4. external beam radiation
Investigation of choice?	Barium swallow
Consequences?	▪ Dysphagia ▪ Squamous cell carcinoma

Gastro-oesophageal reflux disease (GORD)

Definition: Regurgitation of stomach contents into the oesophagus.

Pathophysiology:

- **Decreased lower oesophageal sphincter (LOS) tone.**
- **Primary protective mechanism:** Parasympathetic stimulation of lower circular smooth-muscle fibres prevents reflux.

Causes:

- **Transient LOS relaxation** (most common).
- **Pregnancy**: Progesterone decreases motility.
- **Gastric factors**: Acidity, outlet obstruction, decreased motility.
- **Hiatal hernia**: Seen in ≥90% of severe cases.
- **Obesity**: Leads to transient relaxations of LOS.
- **Lifestyle habits**: Smoking, caffeine, alcohol.
- **Other causes**: Scleroderma, Angle of His enlargement (> 60°).

Clinical Features:

- **Heartburn and regurgitation** when lying down.
- **Non-cardiac chest pain** (common cause).
- **Extra-oesophageal symptoms**: Chronic cough, hoarseness, wheezing.
- **Dental enamel erosion** due to chronic acid exposure.
- **Antacid side effects**: Diarrhoea from magnesium hydroxide.

Investigations:

- **Endoscopy (Upper GI)**:
  - ⇨ For those with alarm features (dysphagia, anemia, weight loss, etc.) or no response to PPI trial.
  - ⇨ Common finding: **Reflux oesophagitis.**
- **24-hour Oesophageal pH monitoring**:
  - ⇨ Confirms GORD in those with persistent symptoms despite PPI therapy.

- **Oesophageal Manometry**:
  ⇨ To exclude motility disorder and assess peristalsis before antireflux surgery.

Treatment:

1. **Lifestyle Changes**:
   ⇨ Smaller meals, avoid eating before bedtime.
   ⇨ Avoid fatty foods, nicotine, alcohol, and certain drugs (calcium-channel blockers).
2. **Pharmacological**:
   ⇨ **Proton Pump Inhibitors (PPI)**:
   - Standard therapy: 20 mg omeprazole OD for 4-8 weeks.
   - High-dose or twice daily if no response to standard dose.

   ⇨ **H2 Receptor Antagonists**:
   - 2nd line if inadequate response to PPI.

   ⇨ **Severe Oesophagitis**:
   - Start with high-dose PPI, move to long-term full-dose PPI as needed.
3. **Surgical (Laparoscopic Nissen Fundoplication)**:
   ⇨ For PPI-refractory cases or intolerance.
   ⇨ **Pre-surgical evaluation**: Recent endoscopy and oesophageal motility/pH study.
4. **Pregnancy**:
   ⇨ 1st line: Lifestyle changes.
   ⇨ 2nd line: Antacids (avoid sodium bicarbonate, magnesium trisilicate).
   ⇨ 3rd line: H2RAs, then PPIs if necessary.

Complications:

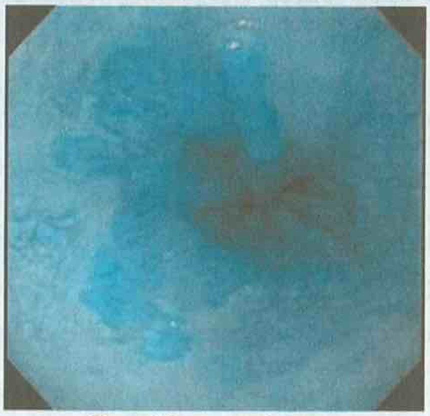
- **Barrett's Oesophagus**: Metaplasia of the lower oesophagus.
- **Oesophageal Strictures**:
  ⇨ Types: Muscular ring (A ring), mucosal ring (B ring - most common).
  ⇨ Often respond to dilation therapy; long-term PPI needed post-dilation.
- **Adenocarcinoma** of the lower oesophagus.

GORD management

- **1st line** → lifestyle changes
  ⇨ don't lie down after eating
  ⇨ avoid spicy foods
  ⇨ eat small servings
- **2nd line** → proton pump inhibitors (omeprazole, lansoprazole) for at least 8 weeks (once daily therapy)
  ⇨ No response: → further diagnostic evaluation
  ⇨ Partial response: → increase the dose to (twice daily therapy)
  ⇨ Good response: → discontinue PPI after 8 weeks
  ⇨ If symptoms recur after discontinuation of PPIs → Maintenance therapy
  ⇨ After 8 weeks of initial treatment, reduce PPI to lowest effective dose
- **3rd line** → H2 receptor antagonists(cimetidine, ranitidine)
- **4th line** → Surgical Nissen fundoplication or hiatal hernia repair

Barrett's oesophagus

Aspect	Details
Definition	Metaplasia of lower oesophageal mucosa ≥ 1 cm above gastroesophageal junction. Normal squamous epithelium is replaced by columnar epithelium (intestinal metaplasia), a premalignant condition caused by chronic GORD.
Risk Factors	Age > 50, male gender, white ethnicity, long-standing GORD, previous oesophagitis, hiatus hernia, central obesity.
Diagnosis	Endoscopic evaluation to visualise columnar epithelium above the gastroesophageal junction. Biopsy confirms intestinal metaplasia (US guidelines) or columnar epithelium (UK guidelines).
Management (Nondysplastic)	Proton pump inhibitors (PPI) and surveillance endoscopy every 3-5 years for <3 cm Barrett's, every 2-3 years for >3 cm.
Management (Low-Grade Dysplasia)	Repeat biopsy in 6 months. If LGD persists, radiofrequency ablation (RFA) is recommended. If ablation is not done, surveillance is recommended every 6 months.
Management (High-Grade Dysplasia)	First-line: Endoscopic resection and RFA. Second-line: Oesophagectomy.
High-Dose PPI Use	High-dose PPI is often used, but there is limited evidence for reducing dysplasia progression or regression.
Prognosis	Increased risk (50-100 fold) of oesophageal adenocarcinoma, though absolute risk remains low (< 1%).



Barrett's oesophagus

Oesophagitis

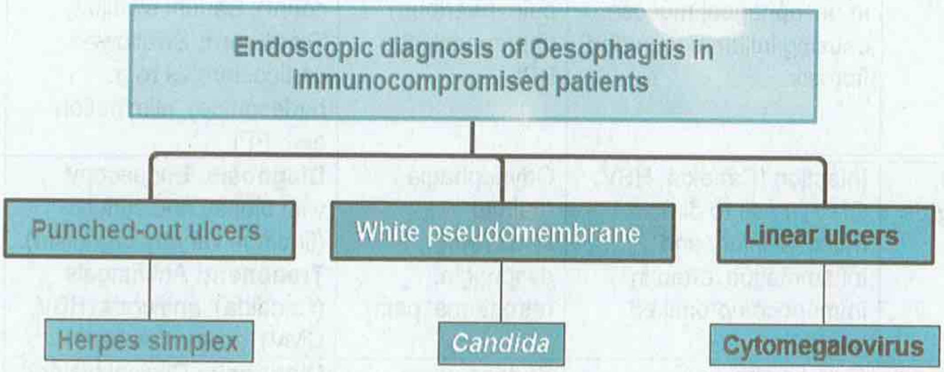
Cause	Pathophysiology	Clinical Features	Diagnosis & Treatment
Reflux (GORD)	Weakened lower oesophageal sphincter allows acid reflux, leading to mucosal damage and inflammation.	Heartburn, regurgitation, dysphagia, chronic cough.	**Diagnosis:** Endoscopy (mucosal erythema/ulcers), pH monitoring, manometry. **Treatment:** Proton pump inhibitors (PPI), lifestyle changes (diet, weight loss).
Eosinophilic Oesophagitis	Allergic reaction results in eosinophil accumulation in oesophageal mucosa, causing inflammation and fibrosis.	Dysphagia, food impaction, chest pain, heartburn unresponsive to PPI.	**Diagnosis:** Endoscopy with biopsy (eosinophil count), Barium swallow. **Treatment:** Swallowed corticosteroids (e.g., budesonide), elimination diet, PPI.
Infectious Oesophagitis	Infection (Candida, HSV, CMV) leads to direct mucosal injury and inflammation, often in immunocompromised hosts.	Odynophagia (painful swallowing), dysphagia, retrosternal pain.	**Diagnosis:** Endoscopy with biopsy and culture (findings vary by organism). **Treatment:** Antifungals (Candida), antivirals (HSV, CMV), supportive care.
Drug-Induced Oesophagitis	Caustic effect of medications or pill lodging causes mucosal damage.	Sudden onset chest pain, odynophagia, dysphagia after taking medication.	**Diagnosis:** Clinical history, endoscopy (ulceration at pill lodging site). **Treatment:** Discontinue offending drug, consider alternatives, PPI for healing.
Radiation Oesophagitis	Radiation damages rapidly dividing mucosal cells, leading to inflammation and ulceration.	Dysphagia, odynophagia, retrosternal pain during or after radiotherapy.	**Diagnosis:** Clinical history, endoscopy (shows erythema, ulceration). **Treatment:** Supportive care, pain management, PPI, topical anaesthetics.

- Oesophagitis in the immunocompromised that presents with punched-out ulcers → Herpes simplex virus-1
- Oesophagitis in the immunocompromised that presents with a white pseudomembrane → *Candida spp.*
- Oesophagitis in the immunocompromised that presents with linear ulcers → Cytomegalovirus

Candida **oesophagitis**

Although oropharyngeal candidiasis may be treated with topical antifungal agents (such as nystatin, clotrimazole, and amphotericin B oral suspension/lozenges) *Candida* oesophagitis requires oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days).

HIV patient presented with painful swallowing difficulty; an upper GI endoscopy shows ulcerative oesophagitis; what is the most likely diagnosis?



Eosinophilic oesophagitis

Definition: Chronic immune-mediated eosinophil-predominant inflammation of the esophageal mucosa

Features: **Episodic oesophageal spasm and intermittent dysphagia**

Diagnosis:

- **Suspect:** if there is a history of food impaction, with persistent dysphagia or Gastroesophageal reflux disease that fails to respond to medical therapy and associated Allergies (e.g., asthma, rhinitis, atopic dermatitis, alimentary allergies)
- **Confirm:** Upper endoscopy with oesophagal **biopsy** → presence of **epithelial infiltrate of ≥ 15 eosinophils** per high-power microscopy field

Treatment

- Diet modification. **Refer for allergy testing** (Eosinophilic esophagitis commonly associated with allergies). Once an antigen is identified, avoidance can improve symptoms
- **Proton pump inhibitors.** If the patient does not respond to a low-dose proton pump inhibitor, increasing the dose to a maximal dose is appropriate before trying other treatment strategies.
- Topical **"swallowed"** corticosteroids for 8 weeks

Patients who present with food impaction, dysphagia, and a history of atopy should undergo an upper endoscopy evaluation with oesophagal biopsy to diagnose eosinophilic esophagitis.

Oesophageal cancer

Epidemiology

- Sex: ♂ > ♀ (3:1)
- Squamous cell carcinoma (SCC) is the most common type worldwide.
- Adenocarcinoma is the most common in the UK and US.

Types

Aspect	Adenocarcinoma	Squamous Cell Carcinoma (SCC)
Epidemiology	Most common in the UK and US. Primarily affects white men.	Most prevalent worldwide. Affects males more than females.
Location	Lower third of the oesophagus.	Upper two-thirds of the oesophagus.
Origin/Histology	Arises from glandular cells in mucus-secreting glands. Associated with intestinal metaplasia (Barrett's oesophagus).	Arises from mucosal squamous cells lining the oesophagus. No glandular origin.
Risk Factors	GORD and Barrett's oesophagus are key. Smoking (twofold risk), obesity, male sex, older age (50-60 years). Not associated with alcohol.	Smoking, alcohol (unlike adenocarcinoma). Dietary factors (low selenium, high red meat, hot liquids). Poor oral hygiene, Tylosis, Achalasia, HPV infection.
Prognosis	Better long-term prognosis after resection than that of SCC.	Poor long-term prognosis after resection. More sensitive to chemo-radiotherapy than adenocarcinoma

Features

- **Early stage:** Often asymptomatic.
- **Late stage:** Progressive dysphagia, initially for solids, then liquids.
- **Hiccups** (tumour spreading to diaphragm).
- **General:** Weight loss, dyspepsia, anaemia.

Diagnosis: **Upper GI endoscopy (first-line)** and then Staging:

- Endoscopic ultrasound (local tumour extent).
- CT of the chest, abdomen, and pelvis for distant metastases.
- PET/CT for detecting occult metastases.

Treatment

- Often unresectable at presentation.
- Chemo-radiotherapy preferred before surgery.
- **Superficial intramucosal cancer:** Endoscopic resection & surveillance.
- **Early-stage cancers**: Oesophagectomy in surgical candidates.
- **Locally advanced disease**: Combined chemo-radiotherapy followed by surgery.
- **High-risk patients:** Combined chemo and radiotherapy.
- **Palliative:** Opioids for pain, nifedipine for oesophageal spasm.

> Oesophageal adenocarcinoma is associated with GORD or Barrett's

Acute upper gastrointestinal bleeding (UGIB)

Definition: bleeding derived from a source proximal to the ligament of Treitz.

Causes: Peptic ulcer, esophagogastric varices, arteriovenous malformation, tumor, esophageal (Mallory-Weiss) tear

Risk factors

- Use of NSAIDs, aspirin, anticoagulants, and antiplatelet agents
- Alcohol abuse, previous GI bleed, liver disease, coagulopathy

Features

- Abdominal pain, hematemesis or "coffee ground" emesis, passing melena/tarry stool
- Tachycardia; orthostatic blood pressure changes suggest moderate to severe blood loss; hypotension suggests life-threatening blood loss (hypotension may be late finding in healthy younger adults)
- Rectal examination is performed to assess stool colour (melena versus hematochezia versus brown)
- Significant abdominal tenderness accompanied by signs of peritoneal irritation (eg, involuntary guarding) suggests perforation

Investigations

- **Crossmatch** for severe bleeding or high-risk patients.
- **Labs:** CBC: haemoglobin concentration (note that haemoglobin may be inaccurate with acute severe haemorrhage), coagulation studies (prothrombin time with INR), liver enzymes (AST, ALT), albumin, RFT, and creatinine
- **Nasogastric lavage** may be helpful if the source of bleeding is unclear (upper or lower GI tract) or to clean the stomach before endoscopy

> **Blood test evidence of upper gastrointestinal haemorrhage**
>
> - **Reactive thrombocytosis**
> - **Urea elevated in excess of creatinine**

Risk assessment (using score calculator)

- **Initially (when the patient first presents) → Blatchford score**
  - ⇨ The score consists of 7 categories :
    - 3 from History: (1) presence of **melena**, (2) **syncope**, (3) **hepatic disease** or **cardiac failure.**
    - 2 from examination: (1) pulse (2) systolic blood pressure
    - 2 from investigations: (1) haemoglobin (2) blood urea nitrogen
  - ⇨ The score ranges from zero to 23. A score of ≤1 indicates a low risk for rebleeding → outpatient management
- **Later (after endoscopy) → Rockall score**

- ⇨ The score consists of **5** categories: (1) age, (2) presence of shock, (3) **comorbidity (e.g., IHD)**, (4) diagnosis, and (5) endoscopic stigmata of recent haemorrhage
- ⇨ Used to determine the prognosis and assess the severity of upper GI bleeds.
- ⇨ Increasing scores are strongly correlated with increasing risk of mortality
- ⇨ Each category is scored between 0 and 2 points, except **co-morbidities of renal or liver failure and metastatic cancer, which has a maximum score of 3 (highest risk of death).**

- **Grades of hypovolaemic shock**

Treatment

- **Do NOT give the patient anything by mouth**
- **Establish two large bore IV lines (16 gauge or larger)**
- **Resuscitation:** Treat hypotension initially with rapid bolus of NS.
- **Transfusion:**
  - ⇨ Avoid over-transfusion with possible variceal bleeding
  - ⇨ Give fresh frozen plasma (FFP) for coagulopathy or after transfusing four units of RBCs.
  - ⇨ Give platelets for thrombocytopenia (platelets <50,000) or platelet dysfunction (e.g., chronic aspirin therapy) or after transfusing four units of RBCs
  - ⇨ Prothrombin complex concentrates on patients who are taking warfarin.
- **For non-variceal bleeding**
  - ⇨ Give a proton pump inhibitor (esomeprazole or pantoprazole, 40 - 80 mg IV)
  - ⇨ IV antibiotic (e.g., ceftriaxone or fluoroquinolone)
- **Consult gastroenterologist, surgeon and interventional radiologist.**
- **Endoscopy**
  - ⇨ should be offered immediately after resuscitation in patients with a severe bleed
  - ⇨ all patients should have an endoscopy within 24 hours
- **For variceal bleeding**
  - ⇨ **Terlipressin**
  - ⇨ **If alcohol dependency is suspected, prescribe Pabrinex**
  - ⇨ **Balloon tamponade** may be performed as a temporising measure for esophagogastric variceal bleeding.
  - ⇨ **Transjugular intrahepatic portosystemic shunts (TIPS)** for variceal bleeding if the above measures fail.

Oesophageal varices

Source of bleeding: Oesophageal varices are tributaries of the left gastric vein, found in the lower 1/3 of the oesophagus. **Lower 1/3 of the oesophagus is drained into the superficial veins lining the oesophagal** mucosa → **left gastric vein** → portal vein.

Acute treatment

- **General:** ABC, resuscitation, correct clotting: FFP, vitamin K
- **Vasoactive agents:** Terlipressin: splanchnic vasoconstrictor →**haemostasis** and prevent **rebleeding**. The most appropriate treatment whilst awaiting urgent endoscopy. **It is contraindicated in those with a history of ischaemic heart disease** as it may precipitate myocardial ischaemia.
- **Prophylactic antibiotics** → reduce mortality in patients with liver cirrhosis.
  - ⇨ Quinolones are typically used.
- **Endoscopic variceal band ligation:** is superior to endoscopic sclerotherapy.
- **Balloon tamponade (e.g., Sengstaken-Blakemore tube, Minnesota tube) if uncontrolled haemorrhage** or delayed endoscopy. Tracheal intubation is necessary if such a device is to be placed; ensure proper placement prior to inflation to avoid oesophagal rupture.
- **Transjugular Intrahepatic Portosystemic Shunt (TIPSS)** if the above measures fail

Prevention

- **Manage or slow the progression of underlying liver disease: e.g., avoiding alcohol and preventing additional insults to the liver (e.g.,** adjusting medications).
- **Pharmacologic prophylaxis:** B. Blockers reduced rebleeding and mortality (propranolol)
- **Endoscopic variceal band ligation (EVL):** is superior to endoscopic sclerotherapy. It should be performed at two-week intervals until all varices have been eradicated. A proton pump inhibitor cover is given to prevent EVL-induced ulceration.
- **Referral for liver transplantation**

Prognosis: Esophageal varices are the most common cause of death in cirrhosis. **Overall mortality from bleeding varices is around 30%.**

> Antibiotic prophylaxis reduces mortality in cirrhotic patients with gastrointestinal bleeding

> Terlipressin - method of action = constriction of the splanchnic vessels

Gastric conditions

Helicobacter pylori

Overview

- *Helicobacter pylori* is a **Gram-negative bacteria** associated with a variety of gastrointestinal problems, principally peptic ulcer disease

Associations

- Peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers)
- gastric cancer (≈ 5%)
  - ⇨ The most common location is the **lesser curvature.**
  - ⇨ Appears as an **ulcer with heaped-up margins.**
- B cell lymphoma of MALT tissue (eradication of H pylori results causes regression in 80% of patients)
- Atrophic gastritis

Diagnosis

Non-invasive methods

Urea breath test

- **The preferred method** for **initial diagnosis** or **confirmation of eradication**
- sensitivity 95-98%, specificity 97-98%
- should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a proton pump inhibitor)

Serum antibody

- sensitivity 85%, specificity 80%
- remains positive after eradication (cannot distinguish between a past and current infection.)

Stool antigen test

- Sensitivity 90%, specificity 95%
- Can be used for initial diagnosis **BUT** NICE guidelines **do not recommend its use to confirm eradication** due to a lack of evidence.

Invasive methods

Rapid urease test (e.g. CLO test)

- Performed on biopsy tissue obtained during endoscopy
- Detects the amount of ammonia produced by H. pylori during urea hydrolysis
- Sensitivity 93-97%, specificity 95-98%
- the false negative rate increases significantly in:
  - ⇨ **recent gastrointestinal haemorrhage**,
  - ⇨ acid suppression therapy and
  - ⇨ recent antibiotic treatment.

Culture of gastric biopsy (Gold standard)

- sensitivity 70%, **specificity 100%**
- Staining and direct microscopic identification (silver stain)
- Curved, gram-negative rods with multiple flagella is the typical appearance of H.pylori.

Gastric biopsy

- Histological evaluation alone, no culture
- Sensitivity 95-99%, specificity 95-99%

Test to confirm eradication :

- **When to test for complete eradication?**
  - ⇨ Re-testing for *Helicobacter pylori* is **indicated only in peptic ulcer** disease to confirm eradication where an initial test is positive.
- **Which test?**
  - ⇨ **Carbon-13 urea breath testing is the only well-validated method for confirming the successful eradication of *Helicobacter pylori*.**

PPIs should be discontinued at least 2 weeks before most H. pylori testing modalities to minimise rates of false-negative results. However, recent PPI treatment does not affect some testing modalities, e.g., histology.

Management

- **First-line treatment**
  - ⇨ Not allergic to penicillin → PPI + amoxicillin + either clarithromycin or metronidazole.
  - ⇨ Allergic to penicillin → PPI + metronidazole + clarithromycin
  - ⇨ Allergic to penicillin + previous exposure to clarithromycin → PPI + bismuth + metronidazole + tetracycline
- **Re-testing for *H. pylori***
  - ⇨ **Re-testing for *H. pylori* before second-line treatment** is considered to confirm eradication as there are serious side effects associated with antibiotics, e.g. *Clostridium difficile* infection, and antibiotic resistance is increasing.
  - ⇨ Eradication therapy is effective in 80-85% of cases and should not be repeated without evidence of treatment failure.
  - ⇨ **the carbon-13 urea breath test is the most accurate method of re-testing for *H. pylori*.**
  - ⇨ NICE guidelines 2019 state: Perform re-testing for H pylori using a **carbon-13 urea breath test.** (**There is currently insufficient evidence to recommend the stool antigen test as a test of eradication**)
- **Second-line treatment** (If still symptomatic after first-line + **positive re-testing for *H. pylori***)
  - ⇨ **Not allergic to penicillin** → PPI + amoxicillin + either clarithromycin or metronidazole (whichever was not used first-line)
  - ⇨ **If there is a previous exposure to clarithromycin and metronidazole** →PPI + amoxicillin + quinolone or tetracycline (whichever has the lowest acquisition cost).
  - ⇨ **Allergic to penicillin + NO previous exposure to a quinolone** → PPI + metronidazole + levofloxacin
  - ⇨ **Allergic to penicillin + previous exposure to a quinolone** → PPI + bismuth + metronidazole + tetracycline.

H. pylori eradication:

- PPI + amoxicillin + clarithromycin, or
- PPI + metronidazole + clarithromycin

Urea breath test - no antibiotics in past 4 weeks, no antisecretory drugs (e.g. PPI) in past 2 weeks

Peptic ulcer

Definition

- **Peptic ulcer disease (PUD)** refers to a break in the mucosal lining of the stomach (gastric ulcer) or duodenum (duodenal ulcer) due to exposure to gastric acid and pepsin.

Epidemiology

- Affects **10%** of people at some point in their lives.
- More common in **men** than women.
- **Duodenal ulcers** are more common than **gastric ulcers**.

Risk Factors

- **Helicobacter pylori infection**: The most common cause of peptic ulcers.
- **Non-steroidal anti-inflammatory drugs (NSAIDs)**: Chronic NSAID use can damage the mucosal lining.
- **Smoking** and **alcohol** use exacerbate ulcer formation.
- **Stress** and **diet** (e.g., caffeine) are not direct causes but may worsen symptoms.

Pathophysiology

- **Increased gastric acid secretion** or **impaired mucosal defense** leads to the formation of ulcers.
- **H. pylori** causes chronic inflammation and weakens the protective mucus lining.
- **NSAIDs** inhibit prostaglandin synthesis, reducing the stomach's ability to protect itself from acid.

Clinical Features

- **Epigastric pain**: The most common symptom.
  - ⇨ **Gastric ulcer**: Pain worsens with eating.
  - ⇨ **Duodenal ulcer**: Pain improves with eating and worsens 2-5 hours after meals.
- **Nausea, vomiting, bloating**, and **indigestion**.
- **Melena** (black, tarry stools) or **hematemesis** (vomiting blood) in cases of ulcer bleeding.

	Gastric ulcer	Duodenal ulcer
Findings common to both	▪ Dyspepsia: postprandial heaviness, early satiety, and gnawing, aching, or burning epigastric pain ▪ Pain relief with antacids ▪ Potential signs of internal bleeding (e.g., anaemia, hematemesis, melena) ▪ Stool sample positive for occult blood (see "Diagnostics" in "Gastrointestinal bleeding")	
Pain and eating	▪ Pain increases shortly after eating → weight loss	▪ Pain is relieved with food intake → weight gain ▪ Pain increases 2–5 hours after eating.
Nocturnal pain	▪ Less common	▪ More common

Complications

- **Gastrointestinal bleeding**: The most common complication, particularly with **posterior duodenal ulcers** (gastroduodenal artery involvement).
- **Perforation**: Leads to peritonitis, causing severe abdominal pain and rigidity.
- **Gastric outlet obstruction**: Due to scarring or swelling, leading to vomiting and inability to eat.
- **Malignancy**: Gastric ulcers carry a small risk of developing into gastric cancer, unlike duodenal ulcers.

Diagnosis

1. **Upper endoscopy (EGD)**: Gold standard for diagnosing peptic ulcers and allowing for biopsy to rule out malignancy.
2. **H. pylori testing**:
   - ⇨ **Urea breath test** or **stool antigen test** to confirm active infection.
   - ⇨ **Biopsy** during endoscopy for histology.
3. **Faecal occult blood test (FOBT)**: Detects hidden blood in the stool, indicating possible bleeding.
4. **Barium swallow**: Can detect ulcers but is less commonly used due to the availability of endoscopy.

Management

Condition	Treatment
H. pylori-positive ulcers	**Triple therapy**: PPI (e.g., omeprazole 20-40 mg daily) + clarithromycin 500 mg + amoxicillin 1 g (or metronidazole if allergic) for 7-14 days.
NSAID-induced ulcers	Discontinue NSAIDs and start **PPI therapy** for 4-8 weeks.
Bleeding ulcers	Endoscopic intervention: **coagulation** or **clipping**. Intravenous PPI is started.
Perforation	Requires emergency **surgical repair.**
Refractory ulcers	Consider repeat **H. pylori testing** and assess for **Zollinger-Ellison syndrome** or **gastric malignancy**.

Prevention

- **Eradication of H. pylori** in affected patients.
- Use of **PPIs** or **H2 blockers** in high-risk patients (e.g., chronic NSAID users) to prevent recurrence.
- **Avoid smoking** and **reduce alcohol consumption** to prevent exacerbation.

Zollinger-Ellison Syndrome (ZES)

Definition: Zollinger-Ellison syndrome (ZES) is a rare disorder characterised by developing one or more gastrinomas. These tumours are typically found in the pancreas or the duodenum (the upper part of the small intestine). Gastrinomas secrete excessive amounts of the hormone gastrin, leading to increased gastric acid production and the formation of peptic ulcers.

Causes:

- Most gastrinomas occur sporadically.
- Around 30% occur as part of MEN type I syndrome

Symptoms:

- Abdominal pain
- Diarrhoea
- Nausea and vomiting
- Weight loss
- Gastrointestinal bleeding
- Peptic ulcers, which may be recurrent and resistant to standard treatments

Diagnosis:

- **Blood Tests:** Measurement of fasting serum gastrin levels. Elevated levels suggest ZES.
- **Secretin Stimulation Test:** Used to confirm the diagnosis by measuring the increase in gastrin levels after secretin administration.
- **Imaging Studies:** CT scan, MRI, and endoscopic ultrasound to locate the gastrinomas.
- **Endoscopy:** To visualise and assess the extent of peptic ulcers.

Treatment:

- **Medications:** Proton pump inhibitors (PPIs) are used to reduce gastric acid production and manage symptoms.
- **Surgery:** Surgical removal of gastrinomas when feasible.
- **Other Treatments:** Somatostatin analogues to control symptoms and chemotherapy for metastatic disease.

Zollinger-Ellison syndrome: **epigastric pain and diarrhoea**

The presence of multiple, large (> 2 cm) ulcers in atypical locations (e.g., the **jejunum**) should raise suspicion of gastrinoma.

Somatostatin

Aspect	Details
Definition	Somatostatin is a peptide hormone that inhibits the secretion of various other hormones.
Source	- Secreted by **D cells** in the pancreas and gastrointestinal tract. - Produced in the hypothalamus, brain, and other tissues.
Forms	- **Somatostatin-14**: Predominant form in the brain. - **Somatostatin-28**: Found in the gut.
Physiological Actions	- **Inhibits Hormone Secretion**: - Growth hormone (pituitary). - Insulin and glucagon (pancreas). - Gastrin, cholecystokinin, secretin, and VIP (GI tract). - **Reduces Gastrointestinal Activity**: - Inhibits gastric acid secretion and gut motility. - Reduces splanchnic blood flow.
Receptors	- **SST1–SST5 receptors**: G-protein coupled receptors mediating somatostatin's effects. - SST2 and SST5 are most relevant in endocrine regulation.

Aspect	Details
Clinical Uses	- **Octreotide/Lanreotide (synthetic analogues)**: - Treat acromegaly (inhibit growth hormone). - Manage carcinoid syndrome, VIPomas, glucagonomas. - **Bleeding Control**: - Gastrointestinal variceal bleeding (reduces splanchnic blood flow).
Side Effects	- Nausea, abdominal pain, diarrhoea. - Gallstones (due to reduced gallbladder motility). - Hyperglycaemia or hypoglycaemia (altered insulin/glucagon secretion).
Regulation	- **Stimulated by**: - High levels of glucose, amino acids, fatty acids. - **Inhibited by**: - Low blood glucose and parasympathetic activity.
Clinical Relevance	- Somatostatinomas (rare tumours) cause diabetes, steatorrhoea, and gallstones due to excessive somatostatin secretion. - Used diagnostically in somatostatin receptor imaging (e.g., neuroendocrine tumours).

Somatostatinoma

Definition:

- A rare neuroendocrine tumour that arises from delta cells in the pancreas or duodenum and secretes excessive somatostatin.

Sites of Origin:

- **Pancreas** (60%)
- **Duodenum and small bowel** (30%)

Clinical Features (Somatostatinoma Syndrome):

- Often **asymptomatic** initially or presents with vague symptoms.
- Classic symptoms from somatostatin overproduction:
  - ⇨ **Diabetes mellitus or glucose intolerance** (inhibits insulin secretion).
  - ⇨ **Gallstones** (due to decreased gallbladder motility).
  - ⇨ **Steatorrhea and diarrhoea** (due to inhibiting pancreatic enzymes and bile secretion).
  - ⇨ **Weight loss and abdominal pain.**

Diagnosis:

- **Laboratory Tests**:
  - ⇨ Elevated **plasma somatostatin levels.**
- **Imaging**:
  - ⇨ **CT, MRI**, or **endoscopic ultrasound** to localise the tumour.
  - ⇨ **Somatostatin receptor scintigraphy (Octreo scan)** to identify metastatic disease.

Management:

1. **Surgical Resection**:
   - ⇨ **Localised disease**: Primary treatment is surgical removal.
   - ⇨ **Metastatic disease**: Surgery may still be consdered to relieve symptoms.
2. **Medical Therapy**:
   - ⇨ **Somatostatin analogues (e.g., octreotide, lanreotide) to control symptoms and slow tumour** growth.

⇨ **Interferon-alpha**: Can be used in some cases to manage symptoms and inhibit tumour growth.

3. **Chemotherapy**:
   ⇨ Considered for **advanced/metastatic disease** if surgery and medical therapy are ineffective.
   ⇨ **Streptozocin and dacarbazine are** commonly used.

Gastroparesis

Definition

- Delayed gastric emptying in the absence of a mechanical obstruction

Causes

- Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery
- Occurs in 10–20% of diabetics after 10 years.

Mechanism

- The major stimulant for gastric motility is "stretch."
- In patients with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility.

Symptoms

- erratic blood glucose control
- chronic nausea, vomiting, epigastric pain, bloating
- early satiety, abdominal fullness, constipation.

Diagnosis

- **Gastric-emptying scan**: Gastric emptying scintigraphy demonstrating ≥10% retention of the radionuclide meal at the end of 4 hours is diagnostic.

Management

Dietary Modifications:

- Small, frequent, low-fat meals with limited fibre content to enhance gastric emptying and minimise symptoms.
- Liquid nutrient-rich meals are often better tolerated than solid food.

Glycaemic Control in Diabetic Patients:

- Optimize blood glucose levels as hyperglycaemia can worsen gastroparesis.

Pharmacologic Therapy:

- **Prokinetic Agents** (to enhance gastric motility):
  ⇨ **Metoclopramide**: FDA-approved for gastroparesis; short-term use recommended due to risk of tardive dyskinesia.
  ⇨ **Domperidone**: Improves symptoms and motility but requires monitoring for cardiac side effects (QT prolongation).
  ⇨ **Erythromycin**: Enhances gastric motility but may develop tachyphylaxis (diminishing effect over time).
- **Antiemetics** for nausea and vomiting: Ondansetron, promethazine, or prochlorperazine may be considered.

Endoscopic or Surgical Interventions:

- For refractory or significant symptoms, Consider **gastric electrical stimulation**, **pyloroplasty**, or **gastrectomy** in severe, medication-resistant cases.

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomiting → Think about a diagnosis of gastroparesis.

Gastric cancer

Definition

- **Gastric cancer** refers to malignancy arising from the lining of the stomach, most commonly **adenocarcinoma**, which accounts for 90% of cases.

Epidemiology

- **5th most common** cancer worldwide and the **3rd leading cause** of cancer death globally.
- More common in **men** than women, particularly over the age of **50**.
- Higher prevalence in **East Asia** (e.g., Japan, South Korea, and China).

Risk Factors

- **Helicobacter pylori infection**: Major risk factor for developing gastric cancer.
- **Diet**: High intake of **smoked, salted, or pickled foods** and low intake of fresh fruits and vegetables.
- **Smoking and alcohol** use.
- **Family history**: A genetic predisposition or **hereditary diffuse gastric cancer (HDGC)** syndrome.
- **Chronic gastritis**, **pernicious anaemia**, and **gastric polyps**.

Pathophysiology

- Chronic inflammation caused by **H. pylori** infection, leading to **gastric atrophy** and intestinal metaplasia, increases the risk of malignant transformation.
- Gastric cancer is classified into **intestinal type** (linked to environmental factors) and **diffuse type** (genetic predisposition).

Types of Gastric Cancer

1. **Adenocarcinoma**: Most common, arises from glandular cells in the stomach lining.
2. **Lymphoma**: Malignant tumours of the stomach's lymphatic tissue.
3. **Gastrointestinal stromal tumours (GIST)**: Rare tumours originating from interstitial cells of Cajal.
4. **Carcinoid tumours**: Neuroendocrine tumours are less common.

Clinical Features

- **Early-stage**: Often asymptomatic or presents with nonspecific symptoms (e.g., indigestion, bloating).
- **Advanced-stage**:
  - ⇨ **Unintentional weight loss.**
  - ⇨ **Epigastric pain** or discomfort.
  - ⇨ **Nausea** and **vomiting**.
  - ⇨ **Dysphagia** (if the tumour is near the gastroesophageal junction).
  - ⇨ **Anaemia** due to chronic blood loss.
  - ⇨ **Melena** (black, tarry stools) or **hematemesis** (vomiting blood).
  - ⇨ **Palpable abdominal mass** (late stage).

Diagnosis

1. **Upper endoscopy (EGD)**: Gold standard for diagnosing gastric cancer; allows for **biopsy**.
2. **Endoscopic ultrasound (EUS)**: Useful for assessing tumour depth and local invasion.
3. **CT or PET scans**: Staging and identifying distant metastases.
4. **Biopsy**: Confirmatory test with histopathological analysis.
5. **Serological markers**: Elevated **CEA** (carcinoembryonic antigen) and **CA 19-9** may indicate advanced disease.

Management

Condition	Treatment
Early-stage localised disease	**Surgical resection** (total or subtotal gastrectomy) with lymph node dissection is the preferred treatment.
Locally advanced or unresectable disease	**Neoadjuvant chemotherapy** or chemoradiotherapy followed by surgery to shrink the tumour before resection.
Metastatic disease	**Palliative chemotherapy** (e.g., FOLFOX, FOLFIRI) to prolong survival. **Targeted therapy** (e.g., trastuzumab for HER2-positive tumours).
Palliative care	Symptom management (e.g., relief of obstruction, pain control, and nutrition support).

Screening

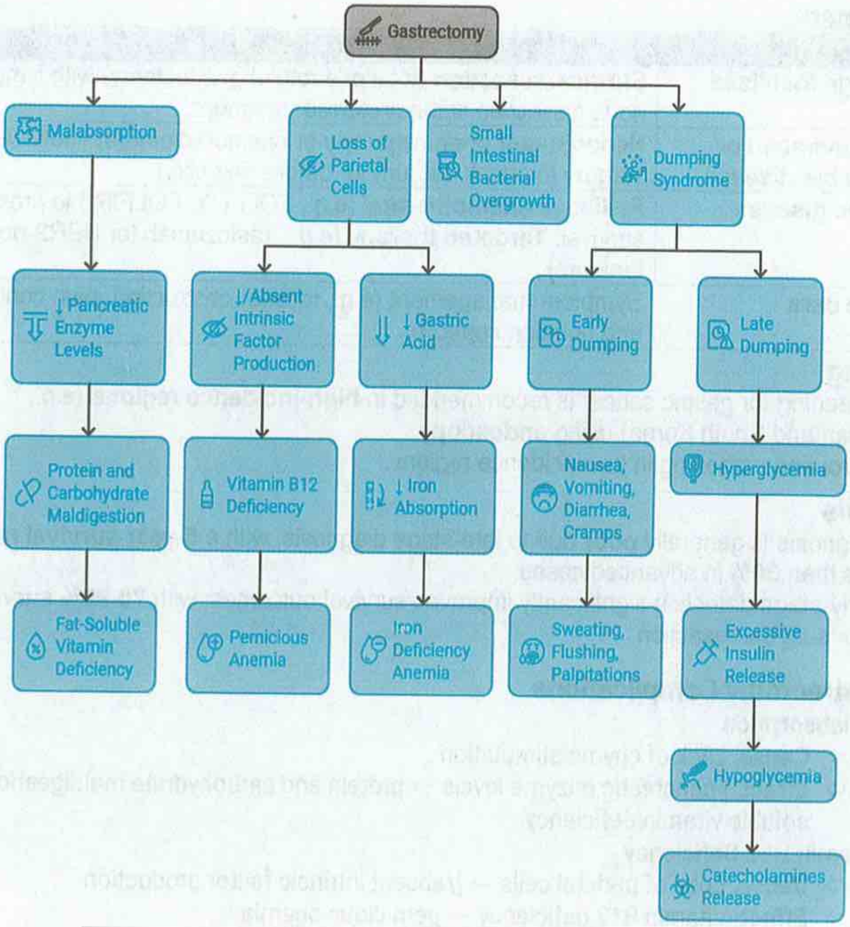
- Screening for gastric cancer is recommended in **high-incidence regions** (e.g., Japan and South Korea) using **endoscopy**.
- No routine screening in low-incidence regions.

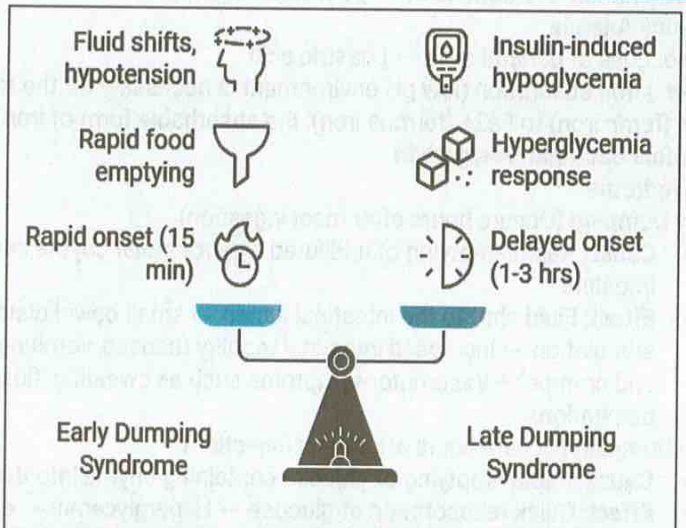
Prognosis

- Prognosis is generally **poor** due to late-stage diagnosis, with a **5-year survival rate** of less than **30%** in advanced cases.
- Early-stage detection significantly improves survival outcomes, with **70-90% survival** after surgical resection.

Post Gastrectomy Complications

1. **Malabsorption**
   - ⇨ **Cause:** Lack of chyme stimulation
   - ⇨ **Effect:** ↓ pancreatic enzyme levels → protein and carbohydrate maldigestion → fat-soluble vitamin deficiency
2. **Vitamin B12 Deficiency**
   - ⇨ **Cause:** Loss of parietal cells → ↓/absent intrinsic factor production
   - ⇨ **Effect:** Vitamin B12 deficiency → pernicious anemia
3. **Iron Deficiency Anemia**
   - ⇨ **Cause:** Loss of parietal cells → ↓ gastric acid
   - ⇨ **Effect:** ↓ iron absorption (low pH environment is necessary for the reduction of Fe^{3+} (ferric iron) to Fe^{2+} (ferrous iron), the absorbable form of iron)
4. **Small Intestinal Bacterial Overgrowth**
5. **Dumping Syndrome**
   - ⇨ **Early Dumping** (Occurs hours after meal ingestion)
     - **Cause:** Rapid emptying of undiluted hyperosmolar chyme into the small intestine
     - **Effect:** Fluid shift to the intestinal lumen → small bowel distention → vagal stimulation → increased intestinal motility (nausea, vomiting, diarrhoea, and cramps) + Vasomotor symptoms such as sweating, flushing, and palpitations
   - ⇨ **Late Dumping** (Occurs hours after meal ingestion)
     - **Cause:** Rapid emptying of glucose-containing chyme into the small intestine
     - **Effect:** Quick reabsorption of glucose → Hyperglycemia → excessive release of insulin → Hypoglycemia and release of catecholamines → signs of hypoglycemia (e.g., hunger, tremor, light-headedness)





Comparing early and late dumping syndromes.

Gastric adenocarcinoma - signet ring cells

Always rule out malignancy in patients with acanthosis nigricans.

Gastric MALT Lymphoma

Aspect	Details
Definition	A low-grade **extranodal marginal zone B-cell lymphoma** arising from the mucosa-associated lymphoid tissue (MALT) in the stomach.
Aetiology	- Strongly associated with **Helicobacter pylori (H. pylori)** infection. - Autoimmune diseases (e.g., Sjögren's syndrome, Hashimoto's thyroiditis).
Pathophysiology	- Chronic H. pylori infection induces inflammation and lymphoid tissue proliferation. - Malignant transformation occurs in B-cells of MALT.
Clinical Features	- Dyspepsia (most common). - Epigastric pain. - Weight loss, nausea, or vomiting (less common). - GI bleeding (rare).
Diagnosis	- **Endoscopy**: Mucosal abnormalities (ulcers, nodules, thickened folds). - **Biopsy**: Histology confirms lymphoma. - **H. pylori Testing**: Urea breath test, stool antigen, or biopsy-based tests. - **Staging**: CT scan, endoscopic ultrasound (EUS), or PET scan for spread.
Treatment	- **First-Line Therapy**: - **H. pylori Eradication**: Triple therapy (PPI + clarithromycin + amoxicillin/metronidazole). - **Second-Line Therapy** (if unresponsive): - Radiotherapy for localized disease. - Rituximab or chemotherapy for advanced cases.
Prognosis	- Excellent prognosis if detected early and treated with H. pylori eradication. - Poorer prognosis with transformation to diffuse large B-cell lymphoma (DLBCL).
Complications	- Progression to high-grade lymphoma (DLBCL). - GI bleeding or perforation.

Gastrointestinal Stromal Tumour (GIST)

Aspect	Details
Definition	A rare mesenchymal tumour of the gastrointestinal (GI) tract arising from **interstitial cells of Cajal**, which are pacemaker cells regulating GI motility.
Epidemiology	- Most common mesenchymal tumour of the GI tract. - Median age at diagnosis: 60 years. - Slight male predominance.
Common Locations	- **Stomach**: ~60–70% of cases. - Small intestine: ~20–30%. - Rarely in oesophagus, colon, rectum, or peritoneum.
Pathophysiology	- **Mutation in KIT proto-oncogene (CD117)** in ~85% of cases. - **PDGFRA mutation** in ~10%. - Leads to constitutive activation of tyrosine kinase, driving tumour growth.
Clinical Features	- **Asymptomatic** (incidental finding on imaging or endoscopy). - **Symptoms**: - GI bleeding (melaena, haematemesis). - Abdominal pain or discomfort. - Palpable mass. - Obstruction or perforation (rare in advanced cases).
Diagnosis	- **Endoscopy or CT Scan**: - Mass in the GI tract, often with heterogeneous enhancement. - **Biopsy**: - Histology shows spindle cells or epithelioid cells. - Immunohistochemistry positive for **CD117 (KIT)** and **DOG1**.
Management	- **Surgery**: - Complete surgical resection for localized disease. - **Adjuvant Therapy**: - **Imatinib (tyrosine kinase inhibitor)** for KIT or PDGFRA-mutant GISTs. - **Palliative Therapy**: - Imatinib for advanced or metastatic disease. - Sunitinib for imatinib-resistant cases.
Prognostic Factors	- Tumour size (>5 cm worse prognosis). - Mitotic rate (>5 per 50 high-power fields). - Tumour location (small bowel worse than stomach).
Complications	- GI bleeding or perforation. - Local invasion or distant metastases (commonly to liver or peritoneum).
Prognosis	- Excellent prognosis with complete surgical resection of small, low-grade tumours. - Advanced disease is managed effectively with tyrosine kinase inhibitors, improving survival.

Dyspepsia

Definition

- **Dyspepsia** refers to a group of symptoms centred around the upper abdomen, including **epigastric pain**, **bloating**, **early satiety**, **nausea**, and **heartburn**. It is often chronic or recurrent.

Initial Assessment

1. **History and Symptoms**:
   - ⇨ Characterise symptoms: **pain location, onset, duration, relationship to meals,** and **associated symptoms** (e.g., weight loss, vomiting).
   - ⇨ **Alarm symptoms**:
     - Unintentional **weight loss**.
     - **Dysphagia** (difficulty swallowing).
     - **Vomiting**.
     - **GI bleeding** (e.g., melena or hematemesis).
     - **Anemia**.
     - Age > **55 years** with new onset dyspepsia.
2. **Physical Examination**:
   - ⇨ Focus on **abdominal exam**, looking for **tenderness**, **masses**, or **organomegaly**.
   - ⇨ Check for signs of **anaemia** (e.g., pallor) or **jaundice**.
3. **Risk Factors**:
   - ⇨ **NSAID** or **aspirin use**.
   - ⇨ **H. pylori infection** (common cause of peptic ulcer disease).
   - ⇨ **Alcohol** consumption and **smoking**.
   - ⇨ **Psychological stress**.

Initial Investigations

1. **Test for H. pylori infection**:
   - ⇨ **Non-invasive tests**: Urea breath test or stool antigen test.
   - ⇨ **Invasive test**: Endoscopy with biopsy for rapid urease testing or histology.
2. **Blood tests**:
   - ⇨ Complete blood count (CBC) to check for **anaemia**.
   - ⇨ Liver function tests to rule out hepatic causes of dyspepsia.
3. **Endoscopy (EGD)**:
   - ⇨ Indicated in patients with **alarm symptoms** or patients **> 55 years** with new onset dyspepsia.
   - ⇨ Can identify **gastritis**, **peptic ulcers**, **gastric cancer**, or **esophagitis**.
4. **Imaging**:
   - ⇨ **Abdominal ultrasound** or **CT scan** may be considered if biliary or pancreatic disease is suspected.

Indications for Endoscopy in Dyspepsia

Indication	Details
Age	Patients **60 years or older** with at least one month of dyspepsia symptoms
Alarm Features	**Bleeding**: Gastrointestinal bleeding or anaemia
	- **Weight Loss**: Unexplained weight loss (more than 10% of body mass) - **Dysphagia**: Progressive dysphagia or odynophagia - **Vomiting**: Persistent vomiting
Family History	Family history of gastrointestinal cancer
Past History	Previous history of oesophagal malignancy, peptic ulcer, lymphadenopathy, or abdominal mass
High-Risk Populations	Patients with a higher risk of upper gastrointestinal malignancy (e.g., patients of Southeast Asian descent)

Management

Condition	Treatment
H. pylori-positive patients	**Triple therapy**: PPI (e.g., omeprazole 20-40 mg daily), clarithromycin 500 mg, and amoxicillin 1 g for 7-14 days.
Functional dyspepsia (no underlying cause found)	**Lifestyle modification**: Reduce alcohol and caffeine intake, quit smoking, and eat smaller, frequent meals. **PPI or H2 blocker trial** for symptom relief.
NSAID-related dyspepsia	Discontinue NSAIDs if possible. **PPI therapy** to heal ulcers or gastritis.
Peptic ulcer disease	PPI for 4-8 weeks; treat underlying **H. pylori** infection if present.
GERD-related dyspepsia	**PPI therapy** for 8 weeks; **lifestyle modifications** (e.g., elevate the head of the bed, avoid eating late at night).
Alarm symptoms or high-risk features	Immediate referral for **endoscopy**.

Malabsorption

Definition

- **Malabsorption** refers to the impaired absorption of nutrients (carbohydrates, fats, proteins, vitamins, and minerals) from the small intestine into the bloodstream, leading to nutrient deficiencies and various clinical symptoms.

Causes

1. **Pancreatic insufficiency**: Inability to produce digestive enzymes (e.g., **chronic pancreatitis, cystic fibrosis**).
2. **Small intestinal mucosal disorders**: **Celiac disease**, **Crohn's disease**, **tropical sprue**.
3. **Bacterial overgrowth**: Excessive bacterial colonisation in the small intestine leads to malabsorption (e.g., **small intestinal bacterial overgrowth - SIBO**).
4. **Bile salt deficiency**: **Liver disease, biliary obstruction**, or **cholestasis** causing fat malabsorption.
5. **Short bowel syndrome**: Surgical resection of a significant portion of the small intestine.
6. **Infections**: **Giardiasis**, **Whipple disease**.

Clinical Features

- **Diarrhoea**: Typically chronic and can be steatorrhea (fatty, foul-smelling stools).
- **Weight loss** despite adequate dietary intake.
- **Nutrient deficiencies**:
  - ⇨ **Fat malabsorption**: Deficiency in fat-soluble vitamins (A, D, E, K), leading to night blindness (vitamin A), bone pain or osteoporosis (vitamin D), and bleeding tendencies (vitamin K).
  - ⇨ **Protein malabsorption**: Edema and muscle wasting.
  - ⇨ **Carbohydrate malabsorption**: Bloating, gas, and diarrhoea (e.g., **lactose intolerance**).
- **Abdominal distension** and **bloating**.
- **Anemia**:
  - ⇨ **Iron deficiency** (microcytic anaemia).
  - ⇨ **Folate/B12 deficiency** (macrocytic anaemia).
- **Osteopenia** or **osteoporosis** due to vitamin D and calcium malabsorption.

Diagnostic Approach

1. **Blood tests**:
   - ⇨ **Complete blood count (CBC)**: Assess anaemia.
   - ⇨ **Iron studies, vitamin levels** (A, D, E, K), and **B12/folate** levels to assess for deficiencies.
   - ⇨ **Electrolytes** and **albumin**: Check for protein malnutrition.
2. **Stool tests**:
   - ⇨ **Faecal fat analysis**: Increased fat in stools (steatorrhea) indicates fat malabsorption.
   - ⇨ **Stool elastase**: Decreased in **pancreatic insufficiency**.
3. **Endoscopy with biopsy**:
   - ⇨ **Upper endoscopy**: To assess for **celiac disease**, **Crohn's disease**, and other small intestinal disorders.
   - ⇨ **Duodenal biopsy**: Gold standard for diagnosing **celiac disease** (villous atrophy).
4. **Breath tests**:
   - ⇨ **Hydrogen breath test**: Useful for diagnosing **lactose intolerance** or **small intestinal bacterial overgrowth** (SIBO).
   - ⇨ **D-xylose test**: Helps differentiate between **mucosal causes** (e.g., celiac) and **pancreatic insufficiency**.
5. **Imaging**:
   - ⇨ **CT scan** or **MRI**: To evaluate for structural causes such as **small bowel obstruction** or **Crohn's disease**.

Management

Condition	Treatment
Pancreatic insufficiency	**Pancreatic enzyme replacement therapy** (e.g., pancrelipase).
Celiac disease	**Gluten-free diet**: Lifelong avoidance of gluten-containing foods (wheat, barley, rye).
Lactose intolerance	**Lactose-free diet** or use of **lactase supplements**.
SIBO	**Antibiotics** (e.g., rifaximin or metronidazole).
Nutrient deficiencies	**Vitamin and mineral supplementation**: Based on specific deficiencies (e.g., vitamin D, calcium, iron, B12).

Fat malabsorption	Low-fat diet and **medium-chain triglycerides (MCT)**, which are easier to absorb.
Short bowel syndrome	**Parenteral nutrition** or **enteral nutrition** if oral intake is insufficient.

Complications

- **Nutritional deficiencies** leading to:
  - ⇨ **Anaemia** (iron, folate, B12 deficiency).
  - ⇨ **Osteoporosis** (vitamin D and calcium deficiency).
  - ⇨ **Coagulopathy** (vitamin K deficiency).
- **Chronic diarrhoea** and **dehydration**.

Jejunal Villous Atrophy

Aspect	Details
Definition	A pathological condition characterised by the flattening or loss of villi in the jejunal mucosa, leading to malabsorption.
Causes	- **Coeliac Disease** (most common): Immune-mediated response to gluten. - **Infectious Causes**: - Giardiasis. - Tropical sprue. - **Autoimmune Conditions**: - Common variable immunodeficiency (CVID). - **Other**: - Crohn's disease. - Drugs (e.g., olmesartan, NSAIDs). - Whipple's disease. - Eosinophilic enteritis.
Pathophysiology	- Destruction of enterocytes and villi due to immune or inflammatory mechanisms. - Results in loss of surface area for nutrient absorption.
Clinical Features	- **Gastrointestinal Symptoms**: - Chronic diarrhoea. - Abdominal bloating and discomfort. - **Nutritional Deficiencies**: - Iron deficiency (anaemia). - Folate and B12 deficiency. - Fat-soluble vitamin deficiencies (A, D, E, K). - **Systemic Symptoms**: - Weight loss. - Fatigue. - Osteomalacia or fractures (vitamin D deficiency).

Aspect	Details
Diagnosis	- **Serological Tests**: - Anti-tissue transglutaminase (tTG) and anti-endomysial antibodies (coeliac disease). - **Endoscopy and Biopsy**: - Jejunal biopsy showing villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. - **Stool Examination**: - For Giardia or Whipple's disease. - **Other Tests**: - Immunoglobulin levels (CVID). - Small bowel imaging for structural abnormalities.
Management	- **Specific Treatment**: - Gluten-free diet for coeliac disease. - Antibiotics (e.g., metronidazole, tetracycline) for tropical sprue or Whipple's disease. - Anti-parasitic agents (e.g., tinidazole) for giardiasis. - **Supportive Measures**: - Nutritional supplementation (iron, folate, vitamin D). - Corticosteroids for eosinophilic enteritis.
Complications	- Chronic malabsorption. - Osteoporosis or fractures. - Severe nutritional deficiencies. - Increased risk of intestinal lymphoma (e.g., in untreated coeliac disease).

Coeliac disease

Definition

- **Coeliac disease** is an autoimmune disorder triggered by the ingestion of **gluten** (found in wheat, barley, and rye), which leads to **inflammation** and **damage** of the **small intestinal mucosa**.
- It is characterized by **villous atrophy** and **malabsorption**.

Epidemiology

- Affects approximately **1%** of the UK population, though many cases remain undiagnosed.
- Can develop at any age but commonly presents in **childhood** or **early adulthood**.
- More common in **women** than men.

Risk Factors

- **Family history**: Higher risk in individuals with a first-degree relative with coeliac disease.
- **Other autoimmune conditions**: e.g., Type 1 diabetes, autoimmune thyroid disease.
- **Genetics**: Associated with **HLA-DQ2** and **HLA-DQ8** genes.

Clinical Features

- **Gastrointestinal symptoms**:
  - ⇨ **Chronic diarrhoea** (often steatorrhea).
  - ⇨ **Abdominal pain** and **bloating**.
  - ⇨ **Weight loss**.
  - ⇨ **Fatigue**.
  - ⇨ **Nausea** and **vomiting**.

- **Non-GI symptoms:**
  - ⇨ **Iron deficiency anaemia** (unexplained).
  - ⇨ **Osteopenia** or **osteoporosis** due to vitamin D and calcium malabsorption.
  - ⇨ **Dermatitis herpetiformis**: A blistering, itchy skin rash associated with coeliac disease.
  - ⇨ **Mouth ulcers** and **dental enamel defects**.

Complications

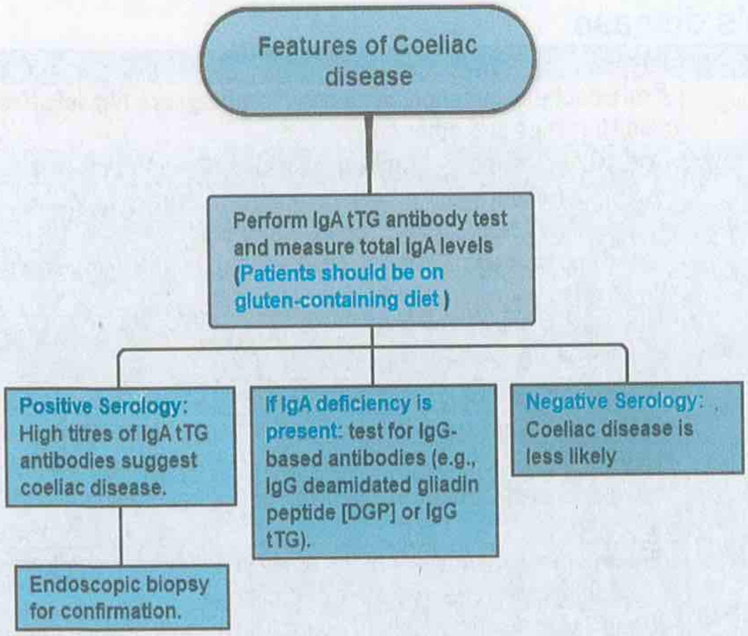
- **Osteoporosis** and **osteomalacia** due to calcium and vitamin D malabsorption.
- **Iron deficiency anaemia** due to malabsorption of iron.
- **Infertility** in both men and women.
- **Small bowel malignancies** (e.g., **enteropathy-associated T-cell lymphoma** and **small bowel adenocarcinoma**).
- **Hyposplenism**: Increased risk of infections, such as **pneumococcal sepsis**.

Screening Recommendations: Screen individuals with:

- **First-degree relatives** of those with coeliac disease.
- **Type 1 diabetes** and other autoimmune conditions.
- **Unexplained iron deficiency anaemia** or **osteoporosis**.
- **Chronic diarrhoea** or **unexplained weight loss**.

Diagnosis

1. **Serology** (first-line test):
   - ⇨ **Tissue transglutaminase antibodies (tTG-IgA)**: Most sensitive and specific screening test.
   - ⇨ **Endomysial antibodies (EMA)**: Used as a confirmatory test in certain cases.
   - ⇨ **Total IgA levels**: To rule out IgA deficiency, which can give false-negative results.
   - ⇨ Patients should continue a **gluten-containing diet** during testing to avoid false negatives.
2. **Duodenal biopsy** (Gold standard for diagnosis):
   - ⇨ Obtained via **upper GI endoscopy**.
   - ⇨ Histological findings include **villous atrophy**, **crypt hyperplasia**, and **increased intraepithelial lymphocytes**.
3. **Genetic testing**:
   - ⇨ **HLA-DQ2** and **HLA-DQ8** testing can be helpful in cases where the diagnosis is uncertain.
   - ⇨ A negative result makes coeliac disease highly unlikely.



Management

Condition	Treatment
Gluten-free diet	Lifelong strict **gluten-free diet** is the mainstay of treatment. This includes avoiding foods containing wheat, barley, and rye.
Dietary education	Referral to a **dietitian** for education on a gluten-free diet is essential.
Vitamin and mineral supplementation	Address deficiencies (e.g., **iron**, **vitamin D**, **calcium**, **folate**, **vitamin B12**).
Follow-up and monitoring	Annual review to assess adherence to the gluten-free diet, monitor symptoms, and screen for complications such as **osteoporosis**.
Dermatitis herpetiformis	Treated with **dapsone** in addition to the gluten-free diet.
Refractory coeliac disease	Considered if symptoms persist despite a gluten-free diet. May require immunosuppressive therapy under specialist care.

Coeliac disease - tissue transglutaminase antibodies first-line test

Whipple's disease

Aspect	Details
Definition	A rare bacterial infection caused by **Tropheryma whipplei** affecting the small intestine and other organs.
Pathophysiology	- **Infection**: Caused by **Tropheryma whipplei**, a gram-positive bacillus.
	- **Immune Response**: The bacteria are incorporated into tissue macrophages, leading to chronic inflammation.
	- **Intestinal Damage**: The bacteria damage the mucosal lining and villi of the small intestine, leading to malabsorption.
	- **Systemic Involvement**: The infection can spread to other organs, including the brain, heart, and eyes.
Symptoms	- **Digestive**: Diarrhoea, abdominal pain, weight loss, malabsorption
	- **Systemic**: Joint pain, fatigue, anaemia, fever, swollen lymph nodes
	- **Neurological**: Difficulty walking, vision problems, confusion, memory loss
Diagnosis	- **Physical Exam**: Look for signs such as stomach tenderness and skin darkening
	- **Biopsy**: Tissue sample from the small intestine showing foamy macrophages with PAS-positive particles
	- **Blood Tests**: Complete blood count (CBC) showing anaemia and low albumin levels
	- **PCR Testing**: Detects Tropheryma whipplei DNA in biopsy specimens or spinal fluid
Treatment	- **Initial Therapy**: Ceftriaxone 2g IV daily or Penicillin G 1.2 million units IV every 4 hours for 2-4 weeks
	- **Long-term Therapy**: Trimethoprim-sulfamethoxazole (Bactrim) 160/800 mg orally twice daily for 1-2 years
	- **Alternative Therapy**: Doxycycline 100 mg orally twice daily combined with Hydroxychloroquine 200 mg orally three times daily for 1-2 years
Prognosis	Potentially life-threatening if untreated, but treatable with antibiotics
Complications	Chronic malabsorption, neurological damage, recurrence of infection

Whipple's disease: jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

Tropical Sprue

Definition	A malabsorption disorder that occurs in tropical regions is characterized by chronic diarrhoea, weight loss, and nutritional deficiencies, particularly of folate and vitamin B12.
Pathophysiology	The exact cause is unknown, but it is thought to be related to a chronic infection or environmental factors in tropical areas, leading to inflammation of the small intestine and impaired nutrient absorption.
Diagnostic Findings	1. **Chronic diarrhoea** lasting more than a month. 2. **Weight loss** and signs of **malnutrition**. 3. **Low serum folate and vitamin B12** levels. 4. **Small bowel biopsy**: Flattened villi and inflammation (similar to celiac disease). 5. **Stool cultures**: Negative for pathogens.
Treatment	1. **Tetracycline**: 250 mg four times daily for 3-6 months (antibiotic to treat possible infection). 2. **Folic acid**: 5 mg daily (to correct folate deficiency). 3. **Vitamin B12 supplementation**: 1,000 mcg intramuscularly monthly or oral dosing for B12 deficiency. 4. **Nutritional support**: High-calorie diet with supplementation for malnutrition.

Irritable bowel syndrome (IBS)

Definition

- **Irritable Bowel Syndrome (IBS)** is a **functional gastrointestinal disorder** characterized by **abdominal pain** or **discomfort** associated with altered bowel habits (diarrhoea, constipation, or both) in the absence of any structural abnormality.
- Symptoms typically last for at least **3 months** and are often exacerbated by stress or dietary factors.

Pathophysiology

- The exact cause is unknown, but IBS is believed to be related to several factors, including:
  - ⇨ **Altered gut motility**: Increased or decreased motility can lead to diarrhoea or constipation.
  - ⇨ **Visceral hypersensitivity**: Patients have an exaggerated response to normal stimuli in the intestines, leading to pain.
  - ⇨ **Gut-brain axis dysregulation**: There is a connection between stress, anxiety, and IBS symptoms due to abnormal communication between the brain and the gut.
  - ⇨ **Altered gut microbiota**: Imbalance in the gut bacteria may contribute to symptoms.
  - ⇨ **Post-infectious IBS**: Some patients develop IBS following a bout of gastroenteritis.

Classification

IBS can be classified into subtypes based on predominant bowel habits:

- **IBS-D**: Diarrhoea-predominant IBS.
- **IBS-C**: Constipation-predominant IBS.

- **IBS-M**: Mixed IBS, where both diarrhoea and constipation alternate.
- **IBS-U**: Unclassified IBS, where symptoms do not fit neatly into other categories.

Diagnostic Features

The **Rome IV criteria** are commonly used for diagnosing IBS. The diagnosis is based on:

1. **Recurrent abdominal pain** at least **1 day per week** in the last 3 months, associated with two or more of the following:
   - ⇨ Related to **defecation**.
   - ⇨ Associated with a change in **stool frequency**.
   - ⇨ Associated with a change in **stool form** (appearance).
2. **Absence of red flag symptoms**: Weight loss, rectal bleeding, anaemia, and nocturnal symptoms should raise suspicion for other conditions and are not typical of IBS.
3. **No structural abnormalities** detected on routine investigations.

Investigations

- Diagnosis is primarily **clinical**.
- Tests may include:
  - ⇨ **Full blood count (FBC)** to rule out anaemia.
  - ⇨ **C-reactive protein (CRP)** or **faecal calprotectin** to exclude inflammatory bowel disease (IBD).
  - ⇨ **Coeliac serology** to rule out coeliac disease.
  - ⇨ **Stool studies** to rule out infection if diarrhoea is predominant.

Treatment

Condition	Treatment
Dietary modifications	**FODMAP diet**: Reduction of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols to reduce symptoms.
Fiber supplementation	**Soluble fiber** (e.g., ispaghula husk 3.5 g dissolved in water) for IBS-C.
IBS-D (Diarrhoea-predominant)	1. **Loperamide**: 2-4 mg after each loose stool (max 16 mg/day). 2. **Bile acid sequestrants** (e.g., cholestyramine) in patients with bile acid malabsorption.
IBS-C (Constipation-predominant)	1. **Laxatives**: Polyethylene glycol to relieve constipation. NICE recommends avoiding lactulose. 2. **Linaclotide**: 290 mcg once daily for severe constipation.
Abdominal pain/bloating	1. **Antispasmodics** (e.g., mebeverine 135 mg 3 times daily) to reduce bowel spasms. 2. **Peppermint oil**: 187 mg 3 times daily for relief of bloating and pain.
Psychological therapies	1. **Cognitive behavioural therapy (CBT)** or **gut-directed hypnotherapy** for patients with significant anxiety or stress-related IBS.
Probiotics	Probiotic supplements may help improve gut flora and alleviate symptoms—trial for 4 weeks.
Severe cases	**Tricyclic antidepressants (TCAs)** (e.g., amitriptyline 10-50 mg at bedtime) for pain relief.

NICE recommend avoiding lactulose in the management of IBS

Lactose intolerance

Pathophysiology

- In lactose intolerance, **insufficient lactase production leads to undigested lactose passing into the colon,** fermented by bacteria, producing **gas** and **lactic acid**, resulting in symptoms.
- There are three main types:
  1. **Primary lactose intolerance**: A genetically determined decline in lactase production after weaning (common in adults).
  2. **Secondary lactose intolerance**: Due to injury to the small intestine (e.g., **gastroenteritis**, **celiac disease**, or **Crohn's disease**).
  3. **Congenital lactase deficiency**: A rare genetic disorder present at birth.

Key Diagnostic Features: **Symptoms** (within 30 minutes to 2 hours after consuming lactose-containing foods):

- **Bloating**.
- **Abdominal cramps**.
- **Diarrhoea**.
- **Flatulence** (excessive gas).
- **Nausea**.

Investigations

- **Lactose hydrogen breath test**: After lactose ingestion, increased **hydrogen levels** in the breath indicate colonic bacteria fermentation of undigested lactose
- **Lactose tolerance test**: A rise in **blood glucose** levels after ingesting lactose suggests the ability to digest lactose. A minimal or no rise indicates intolerance
- **Elimination diet**: Improvement of symptoms after eliminating lactose confirms the diagnosis.

Complications

- **Calcium deficiency**: Leading to increased risk of **osteoporosis** and **bone fractures**.
- **Vitamin D deficiency**.

Management

Condition	Treatment
Dietary management	- **Lactose-free diet**: Avoidance of lactose-containing foods (milk, cheese, yogurt). - Use **lactose-free dairy products** or **lactose-reduced milk**.
Lactase enzyme supplements	- **Over-the-counter lactase enzyme supplements** (e.g., Lactaid) taken before consuming lactose-containing foods to aid digestion.
Calcium and vitamin D supplementation	- **Calcium** (1000-1200 mg/day) and **vitamin D** supplements (400-1000 IU/day) to prevent deficiencies.
Reintroduction of dairy in small amounts	- Some individuals may tolerate small amounts of lactose in divided doses. Introduce gradually to identify individual tolerance levels.
Probiotics	- **Probiotics** may help improve lactose digestion by altering the gut microbiome. Trial for 4 weeks may benefit some individuals.

Melanosis Coli

Aspect	Details
Definition	A disorder of pigmentation of the bowel wall caused by the accumulation of lipofuscin pigment in macrophages.
Causes	- **Laxative Abuse**: - Associated with anthraquinone laxatives (e.g., senna, cascara sagrada, frangula). - Seen in >70% of persons using anthraquinone laxatives within months of use. - **Not caused by** modern laxatives like liquid paraffin or polyethylene glycol. - Alternative medicines containing anthraquinones also implicated.
Pathophysiology	- Chronic anthraquinone use → injury to colonic epithelium. - Lipofuscin pigment formation and engulfment by macrophages → pigmentation in lamina propria.
Diagnosis	- **Histological Diagnosis**: - Rectal biopsy shows macrophages filled with brown pigment in lamina propria. - **Histology**: Pigment-laden macrophages. - **Macroscopic Appearance**: Black pigmentation or reticulated brown discoloration of bowel mucosa.
Treatment	- **Benign Condition**: - Reversible on stopping anthraquinone laxatives. - No specific therapy required.

Diarrhoea - biospy shows pigment laden macrophages = laxative abuse

Protein-losing enteropathy

Definition

Protein-losing enteropathy (PLE) is an excessive loss of serum proteins into the gastrointestinal tract, resulting in hypoproteinemia, oedema, and, in some cases, pleural and pericardial effusions.

Causes

- **Gastrointestinal Conditions**: Crohn's, ulcerative colitis, celiac disease, bacterial or parasitic infections.
- **Lymphatic System Disorders**: Congenital heart disease, lymphatic obstruction, liver cirrhosis.
- **Other Conditions**: AIDS, lupus, rheumatoid arthritis.

Key Diagnostic Features

- **Symptoms**: Chronic diarrhoea, weight loss, oedema, ascites, pleural and pericardial effusions.
- **Blood test:** Low serum albumin
- **Stool Tests (the diagnostic test)**: Presence of alpha-1-antitrypsin (a plasma protein resistant to degradation by gut proteases and a high level indicates leakage of plasma proteins into the gut)

- **Ruling out alternative causes:** loss in the urine, hepatic synthetic dysfunction
- **Imaging**: Dynamic contrast-enhanced MR lymphangiography to assess lymphatic system.

Treatment

- **Treat the underlying disease.**
- **Medications**: Diuretics and steroids to reduce inflammation.
- **Dietary Changes**: High-protein, low-fat diet.
- **Supplements**: Protein infusions, vitamin and mineral supplements.
- **Surgical Interventions**: Embolization to seal leaking lymphatic channels.

Refeeding syndrome

Definition: Refeeding syndrome (RFS) is a potentially fatal condition characterised by severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally, or parenterally.

Causes:

- **Low Stores of Micronutrients**: Caused by low stores of certain micronutrients in the body, particularly phosphorus, potassium, and magnesium.
- **Shift in Fluid and Electrolytes**: When refeeding begins, cells demand these electrolytes to metabolise the food, causing a severe shift in body chemistry.

Pathophysiology:

- **Insulin Release**: Exogenously administered glucose results in insulin release, leading to rapid uptake of glucose, potassium, phosphate, and magnesium into cells, with dramatic falls in extracellular concentrations.
- **Fluid Retention**: Sodium and fluid retention can occur, leading to complications such as oedema and heart failure.

Key Diagnostic Features:

- **Electrolyte Changes**: Hypophosphatemia, hypokalemia, and hypomagnesemia.
- **Fluid-Balance Abnormalities**: Abnormal glucose metabolism and fluid retention.
- **Symptoms:** Chronic diarrhea, weight loss, edema, ascites, pleural and pericardial effusions.

Prevention:

- **Recognize Patients at Risk**: Identify patients at high risk of developing refeeding syndrome.
- **Electrolyte and Vitamin Supplementation**: Provide adequate electrolyte, vitamin, and micronutrient supplementation.
- **Gradual Energy Restoration**: Cautious and gradual increase in caloric intake.
- **Monitoring**: Careful monitoring of critical laboratory indices.
- **Fluid Resuscitation**: Careful fluid resuscitation to manage fluid balance.

Treatment:

- **Electrolyte and Vitamin Supplementation**: Providing adequate electrolyte, vitamin, and micronutrient supplementation.
- **Gradual Energy Restoration**: Cautious and gradual increase in caloric intake.
- **Monitoring**: Careful monitoring of critical laboratory indices.

> Give 50% of normal energy intake in starved patients (> 5 days) to avoid refeeding syndrome

Mesenteric ischaemia

Definition

- **Mesenteric ischaemia** refers to reduced blood flow to the **small or large intestine**, leading to ischemic injury and inflammation.
- **Ischaemic colitis** is a form of **mesenteric ischaemia** affecting the **colon**, typically the **splenic flexure** and **descending colon**.

Types

1. **Acute mesenteric ischaemia**: Sudden onset, often due to embolism or thrombosis.
2. **Chronic mesenteric ischaemia**: Gradual due to atherosclerosis in mesenteric vessels.
3. **Ischaemic colitis**: Transient reduction in colonic blood flow, commonly non-occlusive and associated with low flow states.

Causes

1. **Arterial occlusion**:
   - ⇨ **Embolism** (e.g., from atrial fibrillation, valvular heart disease).
   - ⇨ **Thrombosis** (e.g., atherosclerosis, plaque rupture).
2. **Venous occlusion**:
   - ⇨ **Mesenteric venous thrombosis** due to hypercoagulable states (e.g., malignancy, sepsis).
3. **Non-occlusive ischaemia**:
   - ⇨ Low-flow states (e.g., **heart failure, hypotension, shock**).

Key Diagnostic Features

- **Clinical presentation**:
  - ⇨ **Acute mesenteric ischaemia**:
    - **Sudden onset of severe abdominal pain**, often **disproportionate** to physical findings.
    - **Nausea, vomiting,** and **diarrhoea**.
    - **Bloody stools** may occur later in the disease course.
  - ⇨ **Chronic mesenteric ischaemia**:
    - **Postprandial abdominal pain** (intestinal angina).
    - **Weight loss** due to fear of eating (food avoidance).
  - ⇨ **Ischaemic colitis**:
    - **Mild to moderate abdominal pain** (often in the left lower quadrant).
    - **Bloody diarrhoea** or passage of bloody stools.

Investigations

- **CT angiography**: First-line imaging for suspected acute or chronic mesenteric ischaemia, identifying occlusion or reduced perfusion
- **Colonoscopy**: Useful in diagnosing **ischaemic colitis**, showing pale mucosa, ulceration, or necrosis.
- **Lactate levels**: Elevated in acute mesenteric ischaemia due to tissue hypoperfusion.
- **Abdominal X-ray**: May show thumbprinting (indicative of mucosal oedema) in **ischaemic colitis**.

Complications

- **Bowel infarction**: Leading to perforation, sepsis, and death.
- **Stricture formation**: Particularly after ischaemic colitis.
- **Sepsis**: Due to necrosis of bowel tissue.

Management

Condition	Treatment
Acute mesenteric ischaemia	1. **Urgent surgery** for revascularisation or bowel resection if infarction occurs. 2. **Thrombolysis** or **embolectomy** in cases of arterial embolism or thrombosis. 3. **Anticoagulation** for venous thrombosis (e.g., heparin).
Chronic mesenteric ischaemia	1. **Endovascular interventions** (e.g., angioplasty, stenting) or **open surgical bypass** to improve blood flow. 2. Lifestyle modification (e.g., smoking cessation) and management of cardiovascular risk factors.
Ischaemic colitis	1. **Supportive care**: IV fluids, bowel rest, antibiotics if secondary infection or sepsis is suspected. 2. **Surgery** only if bowel infarction, perforation, or persistent ischemia occurs.

The two most common symptoms of ischemic colitis are severe abdominal pain and hematochezia (passage of fresh blood through the anus).

Infectious conditions

Small bowel bacterial overgrowth syndrome

Definition

- **Small bowel bacterial overgrowth syndrome** occurs when an **abnormally high number of bacteria** in the small intestine leads to **malabsorption**, **nutrient deficiencies**, and **gastrointestinal symptoms**.

Pathophysiology

- The small intestine typically has fewer bacteria than the colon. In SIBO, there is an **overgrowth of colonic-type bacteria** in the small intestine, which interferes with nutrient digestion and absorption. This results in:
  - ⇨ **Deconjugation of bile acids** leads to fat malabsorption.
  - ⇨ **Fermentation of carbohydrates** causes gas, bloating, and diarrhoea.
  - ⇨ **Damage to the intestinal lining** leads to malabsorption of nutrients (e.g., vitamins, fats, proteins).

Causes

- **Structural abnormalities** of the small intestine (e.g., strictures, diverticula, surgical blind loops).
- **Motility disorders** (e.g., scleroderma, diabetic enteropathy).
- **Immune system deficiencies** (e.g., hypogammaglobulinemia).
- **Gastrointestinal diseases** (e.g., Crohn's disease, celiac disease).

Symptoms

- **Bloating** and **excessive gas**.
- **Chronic diarrhoea**.
- **Abdominal pain** or discomfort.
- **Unintentional weight loss**
- **Steatorrhea** (fatty stools) due to malabsorption.
- **Nutrient deficiencies**: Vitamin B12, iron, fat-soluble vitamins.

Investigations:

- **Hydrogen breath test**: Measures hydrogen/methane production after ingesting lactulose or glucose. Elevated levels indicate bacterial overgrowth
- **Small bowel aspirate**: A culture from a small bowel aspirate is the gold standard but less commonly performed due to its invasiveness.
- **Blood tests**: Check for **vitamin deficiencies** (e.g., vitamin B12) and **anaemia**.

Complications

- **Vitamin deficiencies**: Particularly **vitamin B12** and **fat-soluble vitamins** (A, D, E, K).
- **Unintended weight loss** and **malnutrition**.
- **Osteoporosis** due to calcium and vitamin D malabsorption.

Management

Condition	Treatment
Antibiotics (First-line treatment)	1. **Rifaximin**: 550 mg **twice daily** for 14 days. 2. **Ciprofloxacin**: 500 mg **twice daily** for 10–14 days. 3. **Metronidazole**: 250-500 mg **three times daily** for 10–14 days (alternative).
Nutritional support	1. **Vitamin supplementation**: Especially **vitamin B12, iron,** and **fat-soluble vitamins** (A, D, E, K). 2. **High-protein, low-carbohydrate diet** may help reduce symptoms of bloating and gas.
Prokinetic agents (if motility disorder)	1. **Erythromycin**: 50 mg **twice daily** or **low-dose metoclopramide** to improve gut motility.
Probiotics	May be considered as adjunctive therapy to restore the normal gut flora, though evidence is limited.

Steatorrhoea and flatulence are classic presenting features of small bowel bacterial overgrowth.

Spontaneous bacterial peritonitis (SBP)

Definition: Spontaneous bacterial peritonitis (SBP) is an infection of ascitic fluid that cannot be attributed to any intra-abdominal, ongoing inflammatory, or surgically correctable condition. It is one of the most frequently encountered bacterial infections in patients with cirrhosis.

Causes:

- **Cirrhosis**: Most commonly seen in patients with end-stage liver disease.
- **Risk Factors**: Decompensated hepatic state, low ascitic protein/complement, gastrointestinal bleeding, endoscopic sclerotherapy for oesophageal varices, ascites due to malignancy, renal insufficiency, or congestive heart failure.

Key Diagnostic Features:

- **Symptoms**: Abdominal pain, fever, vomiting, altered mental status, gastrointestinal bleeding.
- **Laboratory Tests**: Ascitic fluid analysis showing an absolute neutrophil count >250 cells/mm^3, whether or not there is culture growth.
- **Imaging**: Bedside leukocyte esterase reagent strip testing of ascitic fluid may be used to rule out SBP.

Treatment:

- **Antibiotics**: The practitioner must be aware of local resistance patterns and administer appropriate empirical antibiotic regimens early on.
  - ⇨ **Cefotaxime**: 2 g IV every 8 hours for 5 days.
  - ⇨ **Ceftriaxone**: 2 g IV daily.
  - ⇨ **Norfloxacin**: 400 mg orally once/day for prophylaxis.
  - ⇨ **Ciprofloxacin**: 750 mg orally weekly for prophylaxis.
  - ⇨ **Trimethoprim-sulfamethoxazole**: Double-strength tablet orally five times per week (Monday through Friday) for prophylaxis.
- **Albumin**: Indicated in treating patients with SBP, particularly for those with renal dysfunction. **Dose**: 1.5 g/kg body weight on day 1, followed by 1 g/kg on day 3.
- **Prophylaxis**: Continuous antibiotic prophylaxis is indicated in patients with an ascitic fluid protein concentration <15 g/L (<1.5 g/dL) or a previous episode of SBP.

Pancreatic conditions

Acute Pancreatitis

Pathophysiology

- **Intrapancreatic activation of enzymes**: Results from pancreatic duct obstruction (e.g., gallstones) or direct injury (e.g., alcohol, drugs) → **Autodigestion** of pancreatic tissue → Inflammatory response with cytokine release.
- **Sequelae of pancreatitis**:
  - ⇨ **Shock**: Cytokine release and vascular injury → Capillary leakage, fluid shifts → Hypotension.
  - ⇨ **Pancreatic necrosis**: Hypotension and poor perfusion → Multi-organ failure and pancreatic necrosis.
  - ⇨ **Hypocalcemia**: Fatty acid release binds calcium → Decreased serum calcium levels.

Causes (Mnemonic: I GET SMASHED)

- **I**: Idiopathic
- **G**: Gallstones (50%)
- **E**: Ethanol (alcohol)
- **T**: Trauma
- **S**: Steroids
- **M**: Mumps (and other viruses like Coxsackie B)
- **A**: Autoimmune (e.g., polyarteritis nodosa)
- **S**: Scorpion venom
- **H**: Hypertriglyceridemia
- **E**: ERCP
- **D**: Drugs (e.g., diuretics, anti-epileptics, antimicrobials)

Clinical Features

- **Severe epigastric pain** radiating to the back.
- **Vomiting, systemic inflammatory response syndrome (SIRS)**, elevated serum **amylase** and **lipase**.
- **Hypocalcemia, elevated bilirubin** (suggests gallstones), and rare signs like **Cullen's sign, Grey Turner's sign**, and **Fox's sign** (skin changes indicating internal bleeding).

Complications

- **ARDS** (acute respiratory distress syndrome)
- **Acute kidney injury**
- **DIC** (disseminated intravascular coagulation)
- **Pancreatic necrosis**, **sepsis**, and **pseudocysts**.

Markers of Severity

- **CRP**: Elevated >150 indicates a poor prognosis.
- **SIRS-based criteria**: Recommended over complex scores (e.g., APACHE II, Ranson's criteria).
- **Ranson's criteria**: Used for prognosis; points are assigned based on factors such as age, WBC, glucose, LDH, AST on admission, and further criteria after 48 hours (e.g., calcium, haematocrit, urea rise).

Investigations

- **Lab tests**: Elevated **amylase** (>3x normal), **lipase** (more specific), **haematocrit**, **WBC**, **CRP**, and **liver enzymes**.
- **Imaging**:
  - ⇨ **Ultrasound**: Initial test to detect gallstones and assess for biliary origin.
  - ⇨ **CT scan**: Only if the diagnosis is uncertain or after 48-72 hours if there is no clinical improvement.
  - ⇨ **Abdominal X-ray**: Rarely used but may show a "sentinel loop" or "colon cut-off" sign.

Management

Treatment	Details
Fluid resuscitation	Aggressive hydration with crystalloids (e.g., saline) to maintain hemodynamic targets.
Analgesia	IV opioids (e.g., fentanyl).
Bowel rest	NPO (nothing by mouth) until pain subsides.
Nutrition	Begin enteral feeding once symptoms improve; parenteral nutrition only if enteral feeds fail.
Gallstone pancreatitis	**ERCP** for cholangitis, followed by **cholecystectomy** during the same admission if stable.
Alcohol-related pancreatitis	Replace **thiamine** and **B vitamins** (e.g., B12, folic acid).
Pancreatic necrosis	Conservative management for sterile necrosis; antibiotics and supportive care for infected necrosis.

Chronic pancreatitis

Definition

- **Chronic pancreatitis** is a **progressive inflammatory disease** of the pancreas, resulting in **permanent structural damage**, **impaired exocrine** and **endocrine function**, and recurrent episodes of abdominal pain.

Causes

1. **Alcohol abuse**: The most common cause in the UK (70-80% of cases).
2. **Idiopathic**: Accounts for a significant proportion of cases where no clear cause is identified.
3. **Genetic mutations**: Such as in the **CFTR** gene (related to cystic fibrosis).
4. **Obstruction**: Due to **pancreatic duct stones**, **strictures**, or **tumours**.
5. **Autoimmune pancreatitis**: Associated with conditions like **IgG4-related disease**.
6. **Hypercalcaemia** and **hyperlipidaemia**: Conditions that increase the risk of pancreatitis.
7. **Recurrent acute pancreatitis**: Frequent acute episodes can eventually lead to chronic pancreatitis.

Diagnostic Features

1. **Clinical Presentation**:
   - **Chronic abdominal pain**: Usually epigastric and radiates to the back; may worsen after meals.
   - **Steatorrhoea**: Fatty, pale stools due to exocrine pancreatic insufficiency.
   - **Weight loss**: Due to malabsorption.
   - **Diabetes mellitus**: Due to endocrine insufficiency.

2. **Investigations**:
   - **Serum lipase and amylase**: Often normal or mildly elevated, unlike in acute pancreatitis.
   - **Faecal elastase**: Low levels (<200 μg/g) indicate exocrine insufficiency.
   - **Imaging**:
     - **CT or MRI**: To detect calcifications, ductal dilatation, or gland atrophy, indicative of chronic pancreatitis.
     - **Endoscopic ultrasound (EUS)**: Highly sensitive for detecting early changes in chronic pancreatitis.
   - **Secretin stimulation test**: Used to assess pancreatic exocrine function.

Complications

1. **Exocrine insufficiency**: Leads to **malabsorption** of fats and fat-soluble vitamins (A, D, E, K) causing **steatorrhoea** and **weight loss**.
2. **Endocrine insufficiency**: Results in **diabetes mellitus** (often termed **Type 3c diabetes** in this context).
3. **Pancreatic pseudocysts**: Fluid collections that can lead to infection or rupture.
4. **Pancreatic ductal adenocarcinoma**: Patients with chronic pancreatitis have an increased risk of developing pancreatic cancer.
5. **Bile duct or duodenal obstruction**: Due to fibrosis and scarring in the pancreatic region.
6. **Chronic pain**: Persistent and debilitating pain often requires long-term management.

Management

Treatment Type	Details
Pain Management	- **Paracetamol**: 500 mg–1 g every 4–6 hours as needed (max 4 g/day). - **NSAIDs** (e.g., **ibuprofen** 400 mg three times daily). - **Opioids** (e.g., **morphine**, **tramadol**) for severe pain. - **Tricyclic antidepressants** (e.g., **amitriptyline**) or **gabapentin** may be used for chronic neuropathic pain.
Pancreatic Enzyme Replacement	- **Creon** (pancrelipase) starting at 25,000–50,000 units per meal, with doses adjusted according to symptom relief and weight gain.
Fat-soluble vitamin supplementation	- **Vitamins A, D, E, and K** should be supplemented as necessary in cases of malabsorption.
Diabetes Management	- **Insulin therapy** may be required for patients with **Type 3c diabetes**.
Alcohol cessation	- Strongly recommended to prevent progression of the disease.
Surgical intervention	- **Pancreatic duct stenting**, **lithotripsy**, or **resection** may be considered in cases of intractable pain, obstruction, or pseudocyst formation.
Endoscopic therapy	- May be used for **ductal drainage** or **pseudocyst drainage**.

Key Points:

- **Chronic pancreatitis** is a long-term inflammatory condition primarily caused by **alcohol abuse** and leads to progressive **pancreatic dysfunction**.
- Diagnosis involves imaging (e.g., **CT**, **MRI**, **EUS**) and **pancreatic function tests** (e.g., faecal elastase).
- Management includes **pain control**, **enzyme replacement**, **nutritional support**, and potentially **surgical** or **endoscopic interventions** for complications.

Pancreatic cancer

Definition

- **Pancreatic cancer** refers to a **malignant tumour** arising from the **pancreatic tissue**, most commonly an **adenocarcinoma** of the **exocrine glands**. It is a highly aggressive form of cancer with a poor prognosis due to late diagnosis.

Causes and Risk Factors

1. **Smoking**: The most well-established risk factor.
2. **Chronic pancreatitis**: Long-standing inflammation increases the risk of malignancy.
3. **Diabetes mellitus**: Particularly Type 2 diabetes and new-onset diabetes in older adults.
4. **Obesity**: Linked to an increased risk of pancreatic cancer.
5. **Genetic predisposition**:
   - ⇨ Family history of pancreatic cancer.
   - ⇨ BRCA2 mutation carriers.
   - ⇨ **Hereditary pancreatitis**.
6. **Diet**: High intake of red and processed meats may be associated with increased risk.

Diagnostic Features

1. **Clinical Presentation**:
   - ⇨ **Painless jaundice**: Due to obstruction of the common bile duct (typically in head of pancreas tumours).
   - ⇨ **Abdominal pain**: Often radiating to the back, worse when lying down.
   - ⇨ **Weight loss**: Unexplained and significant.
   - ⇨ **Steatorrhoea**: Due to pancreatic exocrine insufficiency.
   - ⇨ **New-onset diabetes**: In older adults, especially with other concerning symptoms.
   - ⇨ **Pruritus**: Secondary to obstructive jaundice.
2. **Investigations**:
   - ⇨ **Blood tests**:
     - **CA 19-9**: A tumour marker that may be elevated in pancreatic cancer, though not specific for diagnosis.
     - **Liver function tests**: May show cholestasis (e.g., elevated bilirubin, alkaline phosphatase).
   - ⇨ **Imaging**:
     - **Abdominal ultrasound**: Often the first investigation, especially in jaundiced patients.
     - **CT scan with contrast**: Gold standard for diagnosis and staging, used to evaluate tumour size, location, and metastasis.
     - **Endoscopic ultrasound (EUS)**: Useful for biopsy and to evaluate smaller lesions not seen on CT.
   - ⇨ **Biopsy**: Confirmatory diagnosis through histological examination via EUS-guided fine-needle aspiration.

Complications

1. **Obstructive jaundice**: Caused by tumour compressing the bile duct.
2. **Pancreatic exocrine insufficiency**: Results in malabsorption and steatorrhoea.
3. **Diabetes mellitus**: May be a late complication due to islet cell destruction.
4. **Metastasis**: Frequently spreads to the liver, lungs, and peritoneum.
5. **Biliary obstruction**: May lead to cholangitis if untreated.

Management

Treatment Type	Details
Surgical Management	- **Whipple procedure (pancreaticoduodenectomy)**: The most common curative surgery for cancers of the pancreatic head. - **Distal pancreatectomy**: For cancers in the body or tail of the pancreas. - Surgery is only possible in early-stage, non-metastatic disease.
Chemotherapy	- **Gemcitabine**: Commonly used as first-line treatment, typically **1000 mg/m² IV** once weekly. - **FOLFIRINOX** (a combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin): Used in advanced cases for higher efficacy.
Radiotherapy	- Often used in combination with chemotherapy (chemoradiotherapy) to manage locally advanced disease.
Palliative Care	- For inoperable or advanced cases, focus on symptom control, including pain management, biliary drainage, and nutritional support.
Endoscopic Stenting	- **Biliary stenting** to relieve obstructive jaundice and pruritus.
Pain Management	- **Opioids** (e.g., morphine, fentanyl) are commonly used for severe pain.
Pancreatic enzyme replacement	- **Creon** (pancrelipase): To manage malabsorption due to exocrine insufficiency (25,000–50,000 units with meals).

Prognosis

- **5-year survival rate**: Less than 10%, largely due to late-stage diagnosis.
- Patients with **early-stage**, resectable disease have better outcomes, but **metastatic pancreatic cancer** has a poor prognosis, often less than 6 months.

Key Points:

- **Pancreatic cancer** is highly aggressive, with risk factors including **smoking**, **chronic pancreatitis**, and **diabetes**.
- Common presentations include **painless jaundice**, **abdominal pain**, and **weight loss**.
- **CT imaging** and **biopsy** are crucial for diagnosis and staging.
- **Surgical resection** is the only curative option, but many patients present with inoperable disease, requiring **chemotherapy** and **palliative care**.

Biliary conditions

Ascending cholangitis

Definition

- **Ascending cholangitis**, also known as **acute cholangitis**, is a **bacterial infection** of the **biliary tree** that typically occurs in the setting of **biliary obstruction** (e.g., from gallstones or strictures). It is a potentially life-threatening condition requiring prompt treatment.

Pathophysiology

- Biliary obstruction (e.g., from **gallstones, tumours, biliary strictures**) leads to **stasis of bile.**
- **Bacterial contamination** of stagnant bile, commonly by gut flora (e.g., **Escherichia coli, Klebsiella, Enterobacter, Enterococcus**), results in infection.
- In severe cases, the infection can ascend the biliary tree into the liver, causing **sepsis** and **multi-organ failure**.

Causes

1. **Gallstones**: The most common cause of biliary obstruction leading to cholangitis.
2. **Biliary strictures**: Post-surgical or secondary to malignancies.
3. **Biliary stents**: Infection from placement of a biliary stent.
4. **Tumours**: Especially **cholangiocarcinoma** and **pancreatic head cancer**.
5. **Parasites**: Rarely, **liver flukes** (e.g., **Clonorchis sinensis**) can cause biliary obstruction and infection.

Diagnostic Features

1. **Charcot's Triad** (classic features):
   - ⇨ **Fever** (often with rigors).
   - ⇨ **Jaundice**.
   - ⇨ **Right upper quadrant pain**.
2. **Reynolds' Pentad** (signs of severe cholangitis with sepsis):
   - ⇨ **Charcot's triad** plus:
   - ⇨ **Hypotension**.
   - ⇨ **Altered mental status** (e.g., confusion, delirium).
3. **Investigations**:
   - ⇨ **Blood tests**:
     - **Raised inflammatory markers**: Elevated **white blood cell count (WBC)**, **C-reactive protein (CRP)**.
     - **Liver function tests**: Elevated **bilirubin, alkaline phosphatase (ALP)**, and **gamma-glutamyltransferase (GGT)** suggest biliary obstruction.
     - **Blood cultures**: Positive in cases of bacteraemia.
   - ⇨ **Imaging**:
     - **Ultrasound**: Initial test to detect biliary dilatation and gallstones.
     - **MRCP (magnetic resonance cholangiopancreatography)**: Non-invasive imaging to assess for biliary obstruction and identify stones or strictures.

- **Endoscopic retrograde cholangiopancreatography (ERCP)**: Both diagnostic and therapeutic; allows visualisation and intervention (e.g., stone removal or stent placement).

Complications

1. **Sepsis**: Bacteria can spread to the bloodstream, leading to septic shock.
2. **Liver abscesses:** Infection spreading from the biliary tree into the liver.
3. **Multi-organ failure**: Due to severe sepsis and hypotension.
4. **Biliary cirrhosis**: Chronic bile duct obstruction and infection may lead to liver cirrhosis over time.

Management

Treatment Type	Details
Intravenous antibiotics	**Broad-spectrum antibiotics** (covering Gram-negative and anaerobic organisms): - **Piperacillin-tazobactam**: 4.5 g IV every 6–8 hours. - **Ceftriaxone** 2 g IV once daily + **metronidazole** 500 mg IV every 8 hours.
Biliary drainage	**ERCP** (endoscopic retrograde cholangiopancreatography): The treatment of choice for biliary decompression via stone extraction, stent insertion, or sphincterotomy. - Perform urgently in severe cases, ideally within 24-48 hours.
Fluid resuscitation	IV fluids to maintain adequate blood pressure and prevent shock (e.g., normal saline or lactated Ringer's).
Pain management	IV **opioids** (e.g., **morphine** or **fentanyl**) for pain relief.
Surgical intervention	**Cholecystectomy**: In cases of gallstone-related cholangitis, removal of the gallbladder may be necessary, ideally after the acute infection has resolved.

Gallstones (Cholelithiasis)

Definition

- **Gallstones** (cholelithiasis) are **solid deposits** formed from **bile components** within the **gallbladder**. They can vary in size and may be asymptomatic or cause significant complications.

Types of Gallstones

1. **Cholesterol stones**:
   - ⇨ The most common type in Western populations.
   - ⇨ Formed due to **supersaturation of cholesterol** in bile.
2. **Pigment stones**:
   - ⇨ **Black pigment stones**: Formed due to excess **bilirubin** in bile (e.g., haemolysis, cirrhosis).
   - ⇨ **Brown pigment stones**: Often associated with **biliary infections** or **parasitic infestations**.

Risk Factors

- **Age**: Incidence increases with age.
- **Sex**: More common in women, especially of childbearing age.
- **Obesity**: Increases cholesterol saturation in bile.
- **Rapid weight loss**: Associated with increased bile cholesterol supersaturation.
- **Pregnancy**: High oestrogen levels increase cholesterol saturation in bile.
- **Oral contraceptive use** or **hormone replacement therapy**.
- **Family history**: Genetic predisposition.
- **Diabetes mellitus.**
- **Liver disease.**

Diagnostic Features

1. **Clinical Presentation**:
   - ⇨ **Asymptomatic**: Most patients remain symptom-free.
   - ⇨ **Biliary colic**: Episodic, severe pain in the **right upper quadrant** (RUQ) or **epigastrium**, often radiating to the back. Typically occurs after eating fatty meals.
   - ⇨ **Nausea** and **vomiting** may accompany the pain.
2. **Investigations**:
   - ⇨ **Ultrasound**: The **first-line imaging** modality, highly sensitive for detecting gallstones.
   - ⇨ **Liver function tests**: May show elevated **bilirubin, alkaline phosphatase** (ALP), or **transaminases** if there is bile duct involvement or inflammation.
   - ⇨ **MRCP (Magnetic Resonance Cholangiopancreatography)**: Used to evaluate the biliary tree in complex cases.
   - ⇨ **Endoscopic ultrasound (EUS)**: For detailed evaluation of the biliary tract, particularly for microlithiasis.

Complications

1. **Cholecystitis**: Inflammation of the gallbladder due to stone obstruction, presenting with fever, RUQ tenderness, and elevated inflammatory markers.
2. **Choledocholithiasis**: Stones in the common bile duct, which may cause **jaundice**, **biliary colic**, and **pancreatitis**.
3. **Ascending cholangitis**: Bacterial infection of the biliary tree, presenting with **fever**, **jaundice**, and **RUQ pain** (Charcot's triad).
4. **Acute pancreatitis**: Occurs if a gallstone obstructs the pancreatic duct.

Management

Treatment Type	Details
Asymptomatic gallstones	**No treatment** typically required.
Symptomatic gallstones	- **Cholecystectomy** (surgical removal of the gallbladder): Recommended treatment for symptomatic gallstones and recurrent biliary colic. - **Laparoscopic cholecystectomy** is the preferred method.
Acute cholecystitis	- **IV antibiotics** (e.g., **ceftriaxone** 2 g daily + **metronidazole** 500 mg every 8 hours). - **Cholecystectomy** after the acute infection has subsided or as an urgent/emergency procedure in severe cases.
Choledocholithiasis	- **ERCP (Endoscopic Retrograde Cholangiopancreatography)**: To remove stones from the common bile duct, often followed by cholecystectomy.

Treatment Type	Details
Pain management	- **NSAIDs** (e.g., **ibuprofen** 400 mg) or **opioids** (e.g., **morphine**) for severe pain.
Bile acid therapy	- **Ursodeoxycholic acid**: Can dissolve small, non-calcified cholesterol stones, but is less commonly used due to the need for long-term treatment and recurrence. Dosage: 8-10 mg/kg/day.

Key Points:

- **Cholesterol stones** are the most common type of gallstones, and many cases remain **asymptomatic**.
- **Biliary colic** is the typical presentation in symptomatic patients, often triggered by fatty meals.
- The **first-line investigation** for diagnosing gallstones is **abdominal ultrasound**.
- **Laparoscopic cholecystectomy** is the preferred treatment for symptomatic gallstones, with **ERCP** indicated for common bile duct stones.

Bile-acid malabsorption

Definition

- **Bile acid malabsorption** (BAM), also known as **bile acid diarrhoea**, is a condition where excessive bile acids reach the colon, causing increased water secretion and resulting in **chronic diarrhoea**. It is commonly associated with various gastrointestinal conditions or may occur idiopathically.

Pathophysiology

- Normally, bile acids are reabsorbed in the terminal ileum and recycled via the enterohepatic circulation. In BAM, **bile acids are not adequately reabsorbed**, leading to excess bile acids in the colon, which stimulates fluid secretion and motility, resulting in **diarrhoea**.

Causes

1. **Ileal disease**: Crohn's disease, radiation injury.
2. **Ileal resection**: Bowel surgery removing part of the terminal ileum.
3. **Idiopathic BAM**: Occurs without any identifiable gastrointestinal disease.
4. **Secondary BAM**: Associated with conditions such as **coeliac disease, chronic pancreatitis**, or **cholecystectomy**.

Diagnostic Features

1. **Clinical Presentation:**
   - ⇨ **Chronic watery diarrhoea** (often mistaken for irritable bowel syndrome with diarrhoea).
   - ⇨ **Urgency** and **faecal incontinence.**
   - ⇨ **Bloating** and **abdominal discomfort.**
2. **Investigations:**
   - ⇨ **SeHCAT scan** (selenium-75 homocholic acid taurine): The gold standard test to measure bile acid retention. A retention rate <15% at 7 days indicates bile acid malabsorption.
   - ⇨ **Blood tests**: May show **elevated serum bile acids** and **vitamin B12 deficiency** in patients with ileal involvement.
   - ⇨ **Faecal bile acid measurement**: May also be used to diagnose BAM but is less commonly performed.

Management

Treatment Type	Details
Bile acid sequestrants	- **Cholestyramine**: First-line treatment; binds bile acids in the gut to prevent diarrhoea. Dose: **4–16 g/day** in divided doses. - **Colesevelam**: Newer bile acid sequestrant with fewer side effects. Dose: **625 mg** once or twice daily.
Dietary adjustments	- **Low-fat diet**: Reducing fat intake can decrease bile acid production and reduce symptoms.
Vitamin supplementation	- Supplementation may be necessary if malabsorption is causing **vitamin deficiencies** (e.g., **vitamin B12**).
Surgical consideration	- In cases where BAM is caused by ileal resection or Crohn's disease, treating the underlying cause is key.

Key Points:

- BAM can occur secondary to **ileal disease**, **idiopathically**, or in association with other gastrointestinal conditions.
- **Chronic watery diarrhoea** is the hallmark symptom.
- Diagnosis is typically confirmed with a **SeHCAT scan**, and treatment with **bile acid sequestrants** like **cholestyramine** or **colesevelam** is effective in controlling symptoms.

Primary biliary cirrhosis

Definition

- **Primary biliary cirrhosis (PBC)**, now commonly referred to as **primary biliary cholangitis**, is a chronic, progressive **autoimmune liver disease** characterised by the destruction of the **small intrahepatic bile ducts**, leading to cholestasis, fibrosis, and ultimately **cirrhosis**.

Epidemiology

- Most common in **middle-aged women** (female-to-male ratio 9:1).
- Usually presents between the ages of **40 and 60**.

Pathophysiology

- Autoimmune-mediated destruction of **intrahepatic bile ducts**, causing **cholestasis**.
- Bile stasis leads to **progressive inflammation**, fibrosis, and cirrhosis.
- Associated with **anti-mitochondrial antibodies (AMA)**, present in 95% of patients, indicating autoimmune involvement.

Risk Factors

1. **Female gender**.
2. **Family history** of PBC or autoimmune diseases.
3. Associated with other **autoimmune conditions** such as:
   - ⇨ **Sjögren's syndrome**.
   - ⇨ **Thyroid disorders**.
   - ⇨ **Rheumatoid arthritis**.
   - ⇨ **Systemic sclerosis**.

Clinical Features

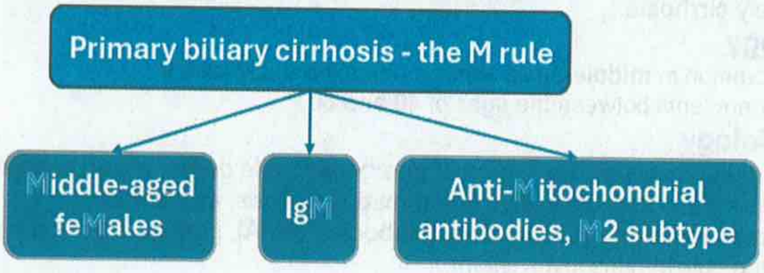
1. **Asymptomatic**:
   - ⇨ Many patients are diagnosed incidentally through abnormal liver function tests.
2. **Early Symptoms**:
   - ⇨ **Fatigue**: One of the most common complaints.

- ⇨ **Pruritus**: Itching, especially at night, before the onset of jaundice.

3. **Late Symptoms** (when cirrhosis develops):
   - ⇨ **Jaundice**: Occurs as liver function deteriorates.
   - ⇨ **Hepatomegaly**: Enlarged liver.
   - ⇨ **Xanthelasma**: Yellowish cholesterol deposits around the eyes.
   - ⇨ **Portal hypertension**: Ascites, varices, splenomegaly.
4. **Other manifestations**:
   - ⇨ **Osteoporosis**: Due to chronic cholestasis.
   - ⇨ **Steatorrhea**: Due to impaired fat absorption.

Diagnostic Features

1. **Liver Function Tests (LFTs)**:
   - ⇨ Elevated **alkaline phosphatase (ALP)** and **gamma-glutamyl transferase (GGT)**, indicating cholestasis.
   - ⇨ Mildly elevated **transaminases** (ALT and AST).
   - ⇨ Elevated **bilirubin** in advanced disease.
2. **Autoantibodies**:
   - ⇨ **Anti-mitochondrial antibodies (AMA)**: Present in 95% of cases.
   - ⇨ **Antinuclear antibodies (ANA)**: Present in 50-70% of patients.
3. **Liver biopsy**:
   - ⇨ Used to assess the **stage** of the disease.
   - ⇨ Shows **inflammation** and **destruction** of bile ducts, with eventual **fibrosis** and cirrhosis.
4. **Imaging**:
   - ⇨ **Ultrasound** to exclude other causes of cholestasis (e.g., bile duct obstruction).
   - ⇨ **FibroScan** to assess the degree of liver fibrosis.



Complications

1. **Cirrhosis**: End-stage liver disease with complications such as portal hypertension and hepatic encephalopathy.
2. **Osteoporosis**: Due to long-term cholestasis.
3. **Vitamin deficiencies**: Fat-soluble vitamins (A, D, E, K) malabsorption.
4. **Hepatocellular carcinoma**: Increased risk in patients with cirrhosis.

NOTES & NOTES

4TH Edition
VOL 3

2025-2026

DR. YOUSIF ABDULLAH HAMAD
MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

FBC
Fareed Book Centre

© Copyright 2025-2026

NOTES AND NOTES

4th Edition

DR. YOUSIF ABDULLAH HAMAD
MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the Copyright Holders.

This book is sold subject to the condition that it shall not, by way of trade or otherwise, be lent, resold, hired out or otherwise circulated without the publisher's prior consent in any form of binding or cover other than that in which it is published and without a similar condition including this condition being imposed on the subsequent purchaser.

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editors, contributors and the publishers have, as far as it is possible, taken care to ensure that the information given in this text is accurate and up-to-date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice. Neither the publisher nor the authors assume any responsibility for any loss or injury and/or damage to person or property arising out of or related to any use of the material contained in this handbook.

Copyright © 2025-2026 All Rights Reserved

Fareed Book Centre
Discover Something New
www.fareedbookcentre.com
156/8, MCB Road, Gulgasht Multan. | 03081401299

SOLE DISTRIBUTOR

Head Office 156/B (Fareed Book Centre) Gulgasht Colony Multan
03081401299
Info@fareedbookcentre.com

Shop No. 9 adjacent Bakhtawar Amir Medical & Dental College Multan
03168081199
Info@fareedbookcentre.com

V-3

Content

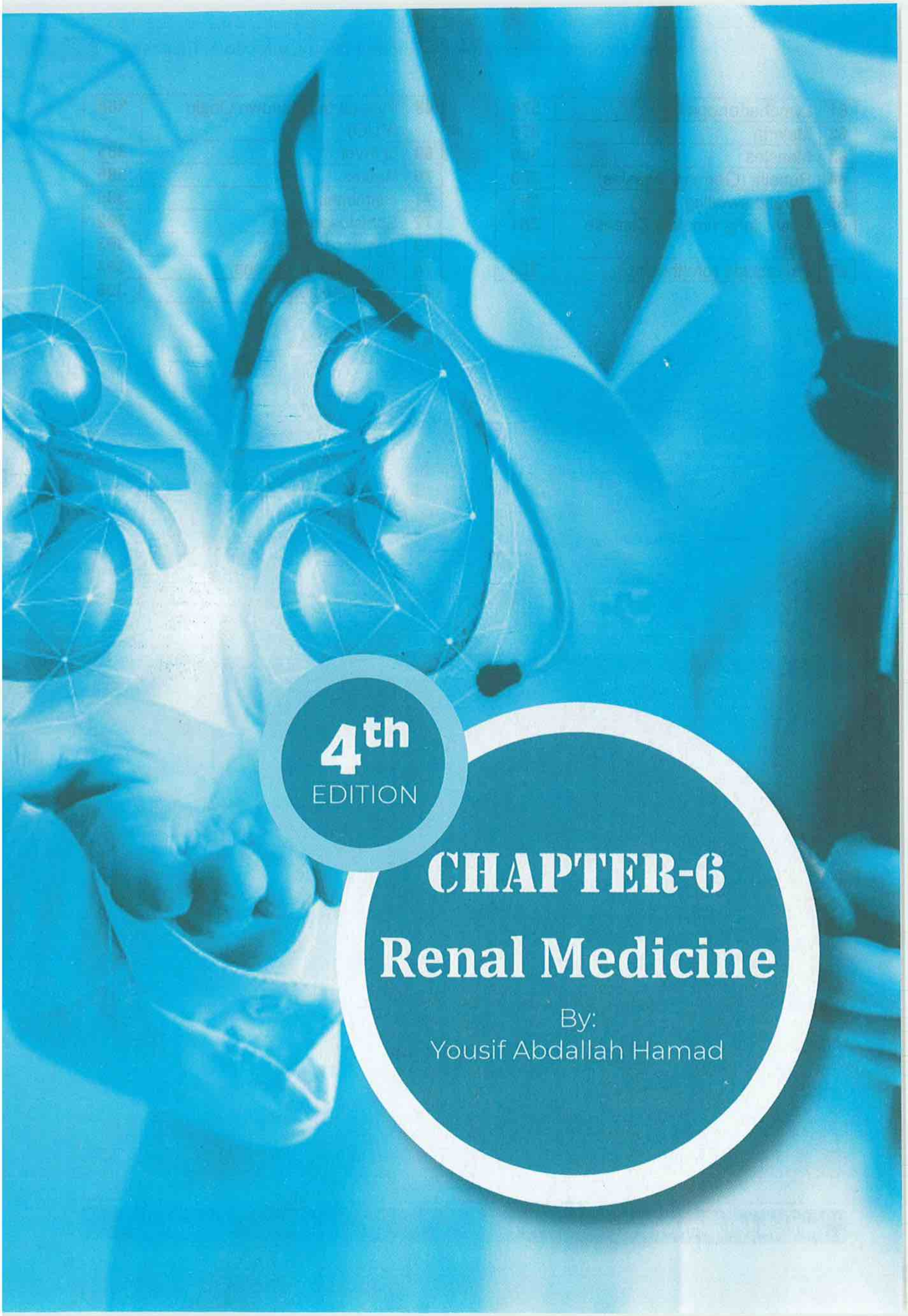
S/N	Topic	Page
	Renal Medicine	1
	Renal Anatomy and Physiology with Clinical Relevance	2
1	Renal Anatomy	2
2	Renal Physiology	2
3	Renin-Angiotensin-Aldosterone System (RAAS)	5
4	Urine Analysis Parameters and Suggested Diagnoses	7
5	Renal Investigations: Indications and Possible Diagnoses	8
6	Renal Biopsy	10
7	Haematuria	11
8	Proteinuria	13
9	Acute interstitial nephritis (AIN)	14
	Acute Kidney Injury (AKI)	16
10	Renal failure	16
11	Acute Kidney Injury (AKI)	18
12	Acute tubular necrosis (ATN)	19
13	Contrast-induced acute kidney injury (CI- AKI)	23
14	Rhabdomyolysis	24
	Chronic Kidney Disease (CKD)	26
15	Chronic Kidney Disease (CKD)	26
16	Diabetic Nephropathy	29
17	Anaemia in Chronic Kidney Disease (CKD)	30
18	Erythropoietin (EPO)	31
19	Renal replacement therapy (RRT)	32
20	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	36
21	Alport's syndrome	39
	Renal tubular defects	41
22	Overview of Renal tubular defects	41
23	Fanconi syndrome	43
24	Bartter and Gitelman syndromes	44
25	Liddle's syndrome	46
26	Renal tubular acidosis (RTA)	46
27	Syndrome of Apparent Mineralocorticoid Excess (SAME)	49
	Glomerulonephritides	50
28	Glomerulonephritides	50
29	Minimal change disease	53
30	Membranous glomerulonephritis	54
31	IgA Nephropathy (Berger's Disease)	56
32	Post-streptococcal glomerulonephritis	57
33	Membrano-proliferative glomerulonephritis (MPGN)	58
34	Rapidly Progressive Glomerulonephritis (RPGN)	60
35	Focal segmental glomerulosclerosis (FSGS)	63
36	Goodpasture's syndrome	62
37	Nephrotic syndrome	64
38	Lupus Nephritis	65
39	Renal vascular disease	67
	Urology and Renal Oncology	69
40	Renal stones	69
41	Hyperoxaluria	71
42	Hypercalciuria	73
43	Cystinuria	75
44	Urinary incontinence (UI)	77
45	Urinary retention	79
46	Benign prostatic hypertrophy (BPH)	80
47	Prostate cancer	82
48	Renal cell cancer (RCC)	83
49	Wilms' Tumour	85
50	Angiomyolipoma	86

51	Bladder cancer	87
52	Urinary tract infection (UTI)	89
53	Renal Tuberculosis	93
54	Vesico-Ureteric Reflux (VUR)	94
55	Urethral Syndrome	95
	Haematology	97
Iron Metabolism		98
1	Iron Absorption, Transport, and Regulation	100
2	Approach to the patient with suspected iron overload	102
3	Haematological changes during pregnancy	105
4	Pathological Red Cell Forms and Diagnostic Associations	106
5	Blood Film Findings and Corresponding Diagnoses	107
6	Pathological White Blood Cell (WBC) Counts and Diagnostic Associations	108
7	Neutropenia	109
8	Leukaemoid Reaction	113
9	Coagulation Abnormalities and associated disorders	114
10	Step-by-Step Approach to Assessing Anemia	115
11	Iron deficiency anaemia (IDA)	117
12	Iron therapy	118
13	Anemia of Chronic Disease	120
14	Thalassaemias	120
15	Pure Red Cell Aplasia (PRCA)	123
16	Macrocytic anaemia	124
17	Pernicious anaemia	125
18	Sickle cell disease (SCD)	128
19	Sideroblastic anaemia	130
20	Haemolytic anaemia	132
21	Autoimmune haemolytic anaemia (AIHA)	134
22	Hereditary spherocytosis	135
23	Glucose-6-phosphate dehydrogenase deficiency(G6PDd)	136
24	Cyanosis Without Hypoxia	137
25	Paroxysmal nocturnal haemoglobinuria (PNH)	139
26	Blood transfusion	140
27	Transfusion-Related Acute Lung Injury (TRALI)	142
28	Plasma Exchange (Plasmapheresis)	143
29	Deep vein thrombosis (DVT)	145
30	Thrombophilia	147
31	Hereditary haemorrhagic telangiectasia (HHT)	150
32	Langerhans cell histiocytosis	152
33	Myelofibrosis	152
34	Myelodysplastic syndrome (MDS)	153
35	Polycythemia	155
36	Elevated RBC Count with Normal Haemoglobin and Haematocrit	156
37	Thrombocytopenia	158
38	Giant Platelet Syndrome: Bernard-Soulier Syndrome (BSS)	160
39	Wiskott-Aldrich syndrome (WAS)	161
40	Idiopathic thrombocytopenic purpura (ITP)	162
41	Thrombotic thrombocytopenic purpura (TTP)	163
42	TTP vs HUS	165
43	Haemolytic uraemic syndrome (HUS)	166
44	Disseminated intravascular coagulation (DIC)	168
45	Thrombocytosis	169
46	Essential thrombocytosis (ET)	170
47	Von Willebrand's disease	171
48	Haemophilia	172
49	Heparin	173
50	Direct Oral Anticoagulants (DOACs)	174
51	Warfarin	176
52	Porphyrias	177
53	Hodgkin's lymphoma (HL)	179
54	Non-Hodgkin's Lymphoma (NHL) Summary	181
55	Burkitt's lymphoma	182
56	Leukemia	184
57	Hairy cell leukaemia (HCL)	188
58	Systemic Mastocytosis (SM)	189

59	Multiple myeloma (MM)	190
60	Monoclonal gammopathy of undetermined significance (MGUS)	193
61	Thymoma	194
62	Tumour lysis syndrome (TLS)	196
63	Waldenström's Macroglobulinemia (WM)	197
64	Tumour markers	198
65	Breast cancer	200
66	Testicular cancer	201
67	Von Hippel-Lindau syndrome (VHL)	203
68	Common licensed monoclonal antibodies	204
69	Commonly Used Chemotherapy Agents	204
70	Granulocyte Colony-Stimulating Factor (G-CSF)	206
71	Palliative Care	207
	Rheumatology	209
1	Bone Remodelling, Osteoclasts, Osteoblasts, and Bone Markers	210
2	Rheumatoid Factor (RF)	211
3	Rheumatoid arthritis (RA)	212
4	Felty's Syndrome	220
5	Seronegative spondyloarthropathies	222
6	Mixed connective tissue disease (MCTD)	223
7	Ankylosing spondylitis	224
8	Avascular necrosis (AVN)	228
9	Behcet's syndrome	228
10	Chronic fatigue syndrome (CFS) (myalgic encephalomyelitis)	230
11	Complex Regional Pain Syndrome (CRPS) vs Compartment Syndrome	231
12	Cryoglobulinaemia	232
13	Dactylitis	236
14	De Quervain's tenosynovitis	237
Monoarticular arthritis		238
15	Gout	239
16	Pseudogout	244
17	Osteoarthritis (OA)	244
18	Septic arthritis	245
19	Avascular necrosis (AVN)	246
20	Paget's disease of the bone	247
21	Psoriatic arthropathy	248
22	Reactive arthritis (Reiter syndrome)	250
23	Amyloidosis	252
24	Sjogren's syndrome	253
25	Systemic lupus erythematosus (SLE)	255
26	Drug-Induced Lupus Erythematosus	257
27	Antiphospholipid syndrome (APS)	259
28	Juvenile Idiopathic Arthritis (JIA) / Still's Disease	260
29	Raynaud's Phenomenon	262
30	Systemic sclerosis (Scleroderma)	264
31	Polymyalgia rheumatica (PMR)	265
32	Differential diagnosis of vasculitis	266
33	Temporal arteritis (Giant cell arteritis (GCA)	269
34	Polyarteritis Nodosa (PAN)	270
35	Granulomatosis with polyangiitis (Wegener's granulomatosis)	270
36	Churg-Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis - EGPA)	271
37	Henoch-Schonlein purpura (HSP)	272
38	Kawasaki disease (KD)	273
39	Takayasu's arteritis	274
40	Buerger's disease (Thromboangiitis obliterans)	274
41	Idiopathic pulmonary hemosiderosis	276
Polyarthritis		277
42	Polyarthritis	277
Myopathies		278
43	Polymyositis	278
44	Dermatomyositis	279
45	Inclusion body myositis (IBM)	281
46	Fibromyalgia (FM)	282
47	Inflammatory Back Pain	285
48	Shoulder problems	286
49	Elbow pain	287

50	Dupuytren's contracture	288
51	Hip pain in adults	288
Immunosuppressants		290
52	Cyclophosphamide (Alkylating Agent)	290
53	Ciclosporin	291
54	Mycophenolate mofetil (MMF)	292
55	Azathioprine	293
56	Biologic Agents	294
57	mTOR Inhibitors (e.g., Sirolimus, Everolimus) Summary	295
58	Glucocorticoid Agents	296
59	Non-steroidal anti-inflammatory drugs (NSAID)	297
Infectious Diseases		299
1	Classification of bacteria	300
2	Gram-positive bacteria	301
3	Staphylococci	302
4	Streptococci (gram-positive cocci)	303
5	Methicillin-resistant *Staphylococcus aureus* (MRSA)	304
6	Cellulitis	304
7	Necrotising fasciitis	306
8	Toxic shock syndrome (TSS)	306
9	Osteomyelitis	307
10	*Enterococcus* (Gram-positive cocci of intestinal origin)	309
11	Gram-positive rod	310
12	Actinomycosis	311
13	Bacillus anthracis (anthrax)	312
14	Clostridium	314
15	Tetanus	315
16	Diphtheria	317
17	Listeria	317
18	Grame-negative bacteria	318
19	Campylobacter	319
20	*Shigella*	319
21	*Escherichia coli*	320
22	Salmonellae	320
23	Enteric (Typhoid and paratyphoid) fever	321
24	Bacterial organism and antibiotic choice	323
25	Meningitis	324
26	Viral encephalitis	328
27	Herpes simplex encephalitis (HSE)	331
28	Progressive multifocal leukoencephalopathy (PML)	332
29	Sepsis	332
30	Tuberculosis (TB)	334
31	Latent tuberculosis infection (LTBI)	337
32	Miliary Tuberculosis (TB)	338
33	Non-tuberculous mycobacterial infections	339
34	Leprosy	339
35	Vaccinations	340
36	Post-exposure prophylaxis (PEP)	341
37	Brucellosis	343
38	Cat scratch disease (CSD)	344
39	Whooping cough (pertussis)	344
40	Cholera	345
41	Chickenpox (Varicella-zoster virus)	345
42	Cytomegalovirus	348
43	Dengue fever	349
44	Yellow fever	350
Sexually Transmitted Infections (STI)		351
45	Human immunodeficiency virus (HIV)	351
46	HIV neurocomplications	355
47	Vaginal discharge	358
48	Genital ulcers (STI)	359
49	Herpes simplex virus	361
50	Syphilis	362
51	*Chlamydia genitourinary infections*	364
52	Gonorrhoea	365
53	Toxoplasmosis	366
54	Acute upper respiratory tract infections: Overview	368
55	Influenza	368
56	Infectious mononucleosis (glandular fever)	370
57	Parvovirus B19	370
58	Visceral leishmaniasis (kala-azar)	371
59	Leptospirosis	372
60	Lyme disease	373

61	Lymphadenopathy	374
62	Malaria	376
63	Measles	380
64	Rubella (German measles)	380
65	Parotid swelling	381
66	Pelvic Inflammatory Disease (PID)	381
67	Psittacosis (ornithosis)	383
68	Pyrexia of Unknown Origin (PUO)	384
69	Q fever	385
70	Rabies	385
71	Helminths	386
72	Schistosomiasis	392
73	Trypanosomiasis	393
74	Rickettsial infections	394
75	Histoplasmosis	396


4th
EDITION
CHAPTER-6
Renal Medicine
By:
Yousif Abdallah Hamad

Renal Anatomy and Physiology with Clinical Relevance

Renal Anatomy

Gross Structure:

- **Kidneys**:
  - Retroperitoneal organs at T12–L3 level.
  - Composed of **cortex** (glomeruli, proximal/distal tubules) and **medulla** (loops of Henle, collecting ducts).
  - **Hilum**: Entry/exit for renal artery, vein, lymphatics, and ureter.

Blood Supply:

- Renal artery → Interlobar arteries → Arcuate arteries → Interlobular arteries → Afferent arteriole.
- Afferent arterioles supply the **glomerulus**; efferent arterioles form the **peritubular capillaries** (cortex) or **vasa recta** (medulla).

Clinical Relevance:

1. **Renal infarction**: Affected by emboli in segmental arteries (no collateral circulation).
2. **Vasa recta**: Key in maintaining medullary osmotic gradient; damage can impair urine concentration (e.g., in shock).

Nephron Structure

- **Functional Unit**: ~1 million nephrons per kidney.
- **Components**:
  - **Glomerulus**: Filters plasma (forms ultrafiltrate).
  - **Proximal Tubule**: Reabsorbs majority of filtered water, glucose, electrolytes.
  - **Loop of Henle**: Establishes medullary concentration gradient.
  - **Distal Tubule**: Adjusts sodium, calcium, and pH.
  - **Collecting Duct**: Final urine concentration regulated by ADH.

Clinical Relevance:

1. **Proximal tubule dysfunction**: **Fanconi syndrome** (loss of glucose, phosphate, bicarbonate).
2. **Loop of Henle dysfunction**: Results in **nephrogenic diabetes insipidus** (impaired urine concentration).
3. **Glomerular damage**: Proteinuria (e.g., nephrotic syndrome).

Renal Physiology

Glomerular Filtration:

- **GFR (Glomerular Filtration Rate)**:
  - Normal: ~120 mL/min/1.73 m^2.
  - Determined by hydrostatic and oncotic pressures.
  - Regulated by:
    - **Myogenic Mechanism**: Adjusts afferent arteriolar tone.
    - **Tubuloglomerular Feedback**: Macula densa senses NaCl levels.

Clinical Relevance:

1. **Low GFR**: Seen in **AKI, CKD**, or shock.
2. **Tubuloglomerular feedback dysfunction**: Implicated in diabetic nephropathy.

Tubular Reabsorption and Secretion:

Segment	Key Functions	Clinical Relevance
Proximal Tubule	Reabsorbs 70% of water, Na^+, K^+, HCO_3^-, glucose, and amino acids.	**Fanconi syndrome** (loss of solutes).
Loop of Henle	Countercurrent multiplier system; descending limb reabsorbs water, ascending limb reabsorbs Na^+.	Impairment leads to dilute or polyuric urine (e.g., loop diuretics).
Distal Tubule	Na^+ reabsorption (aldosterone), Ca^{2+} regulation (PTH).	**Hypocalcaemia** (PTH resistance); **hypercalciuria.**
Collecting Duct	ADH-regulated water reabsorption; acid-base regulation via H^+/HCO_3^- handling.	**Nephrogenic diabetes insipidus, acidosis in distal RTA.**

Hormonal Regulation:

- **Renin-Angiotensin-Aldosterone System (RAAS):**
  - Stimulated by hypovolaemia or low Na^+.
  - Effects: Vasoconstriction, Na^+ reabsorption, K^+ excretion.
- **Antidiuretic Hormone (ADH):**
  - Enhances water reabsorption in the collecting ducts.
- **Parathyroid Hormone (PTH):**
  - Increases Ca^{2+} reabsorption, phosphate excretion in the distal tubule.
- **Erythropoietin (EPO):**
  - Produced in response to hypoxia; stimulates erythropoiesis.

Clinical Relevance:

1. **RAAS overactivation**: Contributes to hypertension in CKD.
2. **ADH resistance**: Causes polyuria in **diabetes insipidus.**
3. **EPO deficiency**: Leads to **anaemia in CKD.**

Acid-Base Regulation

- Kidneys maintain acid-base balance by:
  - Reabsorbing filtered HCO_3^- (proximal tubule).
  - Excreting H^+ as NH_4^+ (ammonium) or $H_2PO_4^-$ (distal tubule).

Clinical Relevance:

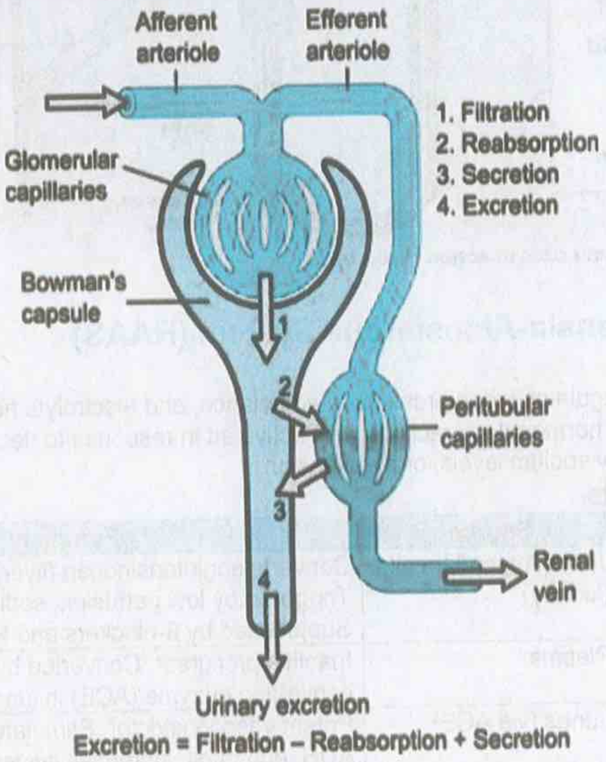
1. **Renal Tubular Acidosis (RTA):**
   - Proximal (Type II): Impaired HCO_3^- reabsorption.
   - Distal (Type I): Impaired H^+ excretion.
2. **Metabolic Acidosis**: Common in CKD.

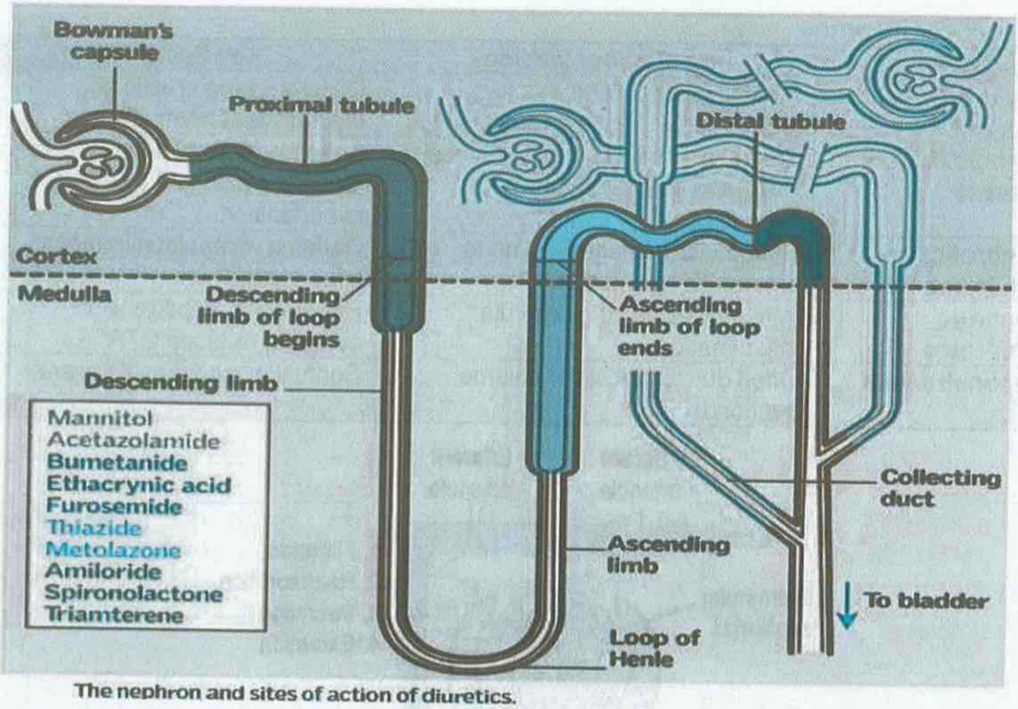
Fluid and Electrolyte Balance

Electrolyte	Renal Regulation	Clinical Relevance
Sodium (Na^+)	Controlled by RAAS and ADH.	**Hyponatraemia** in SIADH; **hypernatraemia** in diabetes insipidus.
Potassium (K^+)	Secreted in distal tubule under aldosterone control.	**Hyperkalaemia** in AKI/CKD; **hypokalaemia** with diuretics.
Calcium (Ca^{2+})	Reabsorbed in proximal/distal tubules; regulated by PTH.	**Hypocalcaemia** in CKD due to reduced active vitamin D (calcitriol).
Phosphate	Excreted in response to PTH; reabsorbed in proximal tubule.	**Hyperphosphataemia** in CKD, contributing to secondary hyperparathyroidism.

Clinical Syndromes

Condition	Key Pathophysiology	Key Features
Acute Kidney Injury (AKI)	Sudden GFR decline due to pre-renal, intrinsic, or post-renal causes.	Oliguria, rising creatinine, electrolyte abnormalities.
Chronic Kidney Disease	Progressive nephron loss, reduced GFR, and compensatory hyperfiltration.	Anaemia, hyperkalaemia, metabolic acidosis, hypertension.
Nephrotic Syndrome	Glomerular damage leading to proteinuria >3.5 g/day.	Oedema, hypoalbuminaemia, hyperlipidaemia.
Nephritic Syndrome	Immune-mediated glomerular inflammation.	Haematuria, hypertension, oedema, reduced GFR.
Hyponatraemia	Often due to SIADH or volume overload.	Confusion, seizures if severe.





The nephron and sites of action of diuretics.

Renin-Angiotensin-Aldosterone System (RAAS)

Definition

- The RAAS regulates blood pressure, fluid balance, and electrolyte homeostasis through a cascade of hormonal interactions. It is activated in response to decreased renal perfusion, low sodium levels, or hypotension.

Key Components

Component	Source	Function
Renin	Juxtaglomerular cells (kidney)	Converts angiotensinogen (liver) → angiotensin I. Triggered by low perfusion, sodium, or BP. Suppressed by β-blockers and NSAIDs.
Angiotensin I	Plasma	Inactive precursor. Converted by angiotensin-converting enzyme (ACE) in lungs → angiotensin II.
Angiotensin II	Lungs (via ACE)	Potent vasoconstrictor. Stimulates aldosterone, ADH, and thirst; increases systemic vascular resistance (SVR) → raises BP.
Aldosterone	Adrenal cortex (zona glomerulosa)	Promotes sodium and water retention, potassium excretion in distal tubules, and contributes to BP elevation.
ADH (Vasopressin)	Posterior pituitary	Increases water reabsorption in collecting ducts, concentrating urine and increasing blood volume.

Mechanism of Action

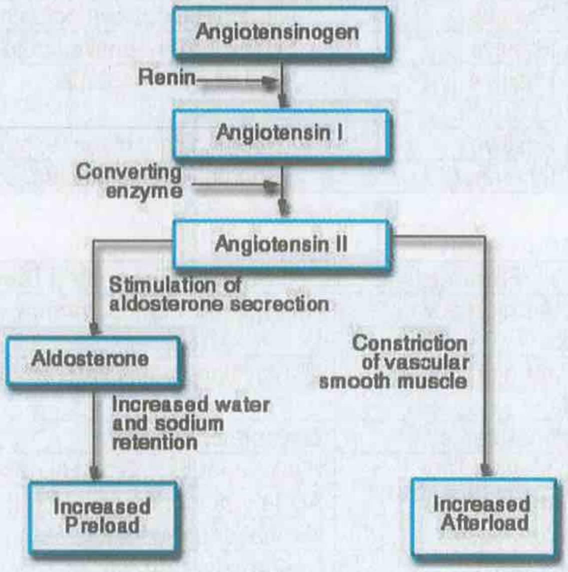
1. **Activation**:
   - Low BP, sodium, or renal perfusion → renin secretion.
   - Sympathetic activation can also stimulate renin release.
2. **Cascade**:
   - Renin converts angiotensinogen → angiotensin I.
   - ACE converts angiotensin I → angiotensin II.
3. **Effects**:
   - Angiotensin II: Vasoconstriction, aldosterone and ADH release, thirst stimulation.
   - Aldosterone: Sodium retention (with water) and potassium excretion.
   - ADH: Water reabsorption, concentrating urine and expanding plasma volume.

Regulatory Factors

- **Stimulation**: Low BP, hyponatremia, renal artery stenosis, sympathetic activity.
- **Inhibition**: High BP, high sodium levels, β-blockers, NSAIDs.

Clinical Relevance

- **Hypertension**: Overactivation leads to high BP; ACE inhibitors/ARBs are effective treatments.
- **Heart Failure**: RAAS contributes to fluid retention and increased afterload.
- **Primary Hyperaldosteronism**: Suppressed renin due to feedback inhibition.



Urine Analysis Parameters and Suggested Diagnoses

1. Physical Appearance

Parameter	Findings	Suggested Diagnosis
Colour	Dark yellow	Dehydration.
	Red or pink	Haematuria, haemoglobinuria, myoglobinuria.
	Brown (cola-coloured)	Glomerulonephritis, myoglobinuria.
	Milky	Pyuria, chyluria.
Clarity	Cloudy	Infection, crystals, or proteinuria.
Odour	Sweet	Diabetic ketoacidosis (DKA).
	Foul	Urinary tract infection (UTI).

2. Chemical Analysis

Parameter	Findings	Suggested Diagnosis
pH	<4.5	Metabolic or respiratory acidosis.
	>8.0	UTI with urea-splitting organisms (e.g., Proteus).
Protein	Positive (>150 mg/day)	Nephrotic syndrome, glomerulonephritis, CKD.
Glucose	Positive	Diabetes mellitus, Fanconi syndrome.
Ketones	Positive	DKA, starvation, prolonged vomiting.
Blood	Positive	Haematuria, haemoglobinuria, myoglobinuria.
Nitrites	Positive	UTI (gram-negative bacteria).
Leukocyte Esterase	Positive	UTI or pyelonephritis.
Bilirubin	Positive	Hepatobiliary disease, haemolysis.
Urobilinogen	Increased	Haemolysis, liver disease.

3. Microscopic Examination

Parameter	Findings	Suggested Diagnosis
RBCs	>3 per high-power field	Haematuria: stones, trauma, glomerulonephritis.
WBCs	>5 per high-power field	UTI, pyelonephritis, interstitial nephritis.
Casts	Red cell casts	Glomerulonephritis.
	White cell casts	Pyelonephritis, interstitial nephritis.
	Granular casts	Acute tubular necrosis (ATN).
	Hyaline casts	Normal or dehydration.
	Fatty casts	Nephrotic syndrome.
Crystals	Uric acid	Gout, tumour lysis syndrome.
	Calcium oxalate	Hyperoxaluria, ethylene glycol poisoning.
	Struvite	Infection with urea-splitting organisms.
	Cystine	Cystinuria (genetic disorder).
Microorganisms	Bacteria	UTI (interpret with nitrites and leukocytes).
	Yeast	Candiduria (immunosuppression, diabetes).

4. Quantitative Tests

Parameter	Findings	Suggested Diagnosis
Urine Protein:Creatinine Ratio (PCR)	>300 mg/g	Nephrotic syndrome.
Urine Albumin:Creatinine Ratio (ACR)	30–300 mg/g	Microalbuminuria: early diabetic nephropathy.
24-Hour Urine Protein	>3.5 g/day	Nephrotic syndrome.

5. Additional Urine Tests

Test	Findings	Suggested Diagnosis
Specific Gravity	<1.010	Dilute urine: diabetes insipidus, renal failure.
	>1.025	Concentrated urine: dehydration, SIADH.
Urinary Sodium	<20 mmol/L	Prerenal AKI.
	>40 mmol/L	Intrinsic renal failure (ATN).
Urinary Osmolality	<350 mOsm/kg	Dilute urine: diabetes insipidus, ATN.
	>500 mOsm/kg	Concentrated urine: prerenal AKI, SIADH.

Key Points for MRCP:

1. **Dipstick results** guide initial diagnosis but must be confirmed with further tests.
2. **Red cell casts** are pathognomonic of glomerulonephritis.
3. **Nitrites and leukocyte esterase** together strongly suggest UTI.
4. **Proteinuria** is a hallmark of nephrotic syndrome and chronic kidney disease.
5. Always correlate urine findings with clinical presentation for accurate diagnosis.

Renal Investigations: Indications and Possible Diagnoses

1. Blood Tests

Investigation	Indication	Possible Diagnosis
Serum Creatinine	Assess renal function; detect AKI or CKD.	Acute kidney injury (AKI), chronic kidney disease (CKD).
Estimated GFR (eGFR)	Evaluate kidney function over time.	CKD staging, renal dysfunction.
Blood Urea Nitrogen (BUN)	Evaluate renal excretory function.	Dehydration (↑ BUN:Creatinine ratio), AKI, CKD.
Electrolytes (Na^+, K^+, Cl^-, HCO_3^-)	Assess for imbalances.	Hyperkalaemia (CKD), hyponatraemia (SIADH), acidosis (renal tubular acidosis).
Calcium and Phosphate	Suspected bone-mineral disorders.	Hyperphosphataemia, hypocalcaemia (CKD-MBD).
PTH (Parathyroid Hormone)	Bone metabolism in CKD.	Secondary hyperparathyroidism in CKD.
ABG (Arterial Blood Gas)	Suspected acidosis or alkalosis.	Metabolic acidosis (renal tubular acidosis, CKD).

2. Urine Analysis

Investigation	Indication	Possible Diagnosis
Urinalysis (Dipstick)	Initial assessment of kidney function.	Proteinuria (nephrotic syndrome), haematuria (glomerulonephritis, UTI).
Urine Microscopy	Evaluate sediment abnormalities.	Red cell casts (glomerulonephritis), WBC casts (pyelonephritis).
Urine Protein:Creatinine Ratio (PCR)	Quantify proteinuria.	Nephrotic syndrome (>300 mg/mmol).
Urine Albumin:Creatinine Ratio (ACR)	Screen for diabetic nephropathy.	Microalbuminuria (early diabetic nephropathy).
24-Hour Urine Collection	Quantify protein or electrolyte excretion.	Nephrotic syndrome (>3.5 g/day), hypercalciuria.
Urine Sodium (Una^+)	Assess volume status and AKI type.	Low Una^+ (<20 mmol/L): prerenal AKI; high Una^+ (>40 mmol/L): ATN.
Urine Osmolality	Assess concentrating ability.	Dilute urine: diabetes insipidus; concentrated urine: SIADH, dehydration.

3. Imaging Studies

Investigation	Indication	Possible Diagnosis
Renal Ultrasound	Initial imaging for renal function.	Hydronephrosis (obstruction), renal cysts, CKD (small kidneys).
CT Kidney, Ureter, Bladder (CT KUB)	Suspected obstruction or stones.	Nephrolithiasis, renal masses, trauma.
CT Abdomen with Contrast	Evaluate renal masses or vascular conditions.	Renal cell carcinoma, renal artery stenosis.
MRI	Contrast contraindication or complex masses.	Polycystic kidney disease, renal vein thrombosis.
Nuclear Renal Scan	Assess differential renal function.	Renal artery stenosis, obstructive uropathy.
DMSA Scan	Evaluate renal scarring in paediatrics.	Reflux nephropathy, pyelonephritis.

4. Specialised Tests

Investigation	Indication	Possible Diagnosis
Renal Biopsy	Evaluate glomerular or unexplained CKD.	Glomerulonephritis, interstitial nephritis, lupus nephritis.
Serum Immunology: ANA, ANCA, Anti-GBM	Suspected autoimmune renal disease.	Lupus nephritis (ANA), vasculitis (ANCA), Goodpasture syndrome (Anti-GBM).
Complement Levels (C3, C4)	Evaluate immune-mediated diseases.	Low C3/C4: lupus nephritis, post-infectious GN.
Myeloma Screen: Serum protein electrophoresis, urine Bence Jones protein	Suspected myeloma-related renal dysfunction.	Light chain cast nephropathy (myeloma kidney).
Serum Free Light Chains	Assess for monoclonal gammopathies.	Myeloma kidney, amyloidosis.
Plasma Renin and Aldosterone	Hypertension with suspected renal origin.	Primary aldosteronism, renal artery stenosis.

5. Functional Tests

Investigation	Indication	Possible Diagnosis
Creatinine Clearance	Estimate GFR if eGFR unreliable.	CKD, reduced kidney function.
Fractional Excretion of Sodium (FENa)	Differentiate AKI type.	Low FENa (<1%): prerenal AKI; high FENa (>2%): ATN.
Water Deprivation Test	Assess concentrating ability of kidneys.	Central or nephrogenic diabetes insipidus.

Renal Biopsy

Indications:

1. Glomerular Diseases:

- Nephrotic Syndrome:
  - Adults: To identify causes (e.g., membranous nephropathy, minimal change disease, FSGS).
  - Children: If resistant to corticosteroids.
- Nephritic Syndrome:
  - To diagnose glomerulonephritis (e.g., post-infectious GN, IgA nephropathy, lupus nephritis).

2. Renal Failure:

- Acute Kidney Injury (AKI):
  - Unexplained or persistent AKI not due to pre-renal or post-renal causes.
  - Suspected acute glomerulonephritis or acute interstitial nephritis.
- Chronic Kidney Disease (CKD):
  - Rapid progression or unclear aetiology (e.g., proteinuria without diabetes).

3. Systemic Diseases with Renal Involvement:

- Lupus nephritis (SLE).
- ANCA-associated vasculitis.
- Goodpasture syndrome (Anti-GBM disease).
- Amyloidosis.

4. Transplant Evaluation:

- Diagnosis of rejection, recurrent disease, or drug toxicity in kidney transplants.

Contraindications:

Absolute:

- Active bleeding disorders.
- Uncontrolled hypertension.
- Solitary kidney (except in transplanted kidneys).
- Active infection near the biopsy site.

Relative:

- Small kidneys on imaging (advanced CKD).
- Multiple cysts (e.g., polycystic kidney disease).
- Pregnancy.

Procedure:

1. Preparation:
    - Stop anticoagulants (e.g., warfarin, DOACs) prior to the procedure.
    - Check coagulation profile (PT, aPTT, INR) and platelet count.
    - Ensure adequate blood pressure control.
2. Techniques:
    - **Percutaneous Biopsy** (most common):
        - Ultrasound-guided or CT-guided.
    - **Open Surgical Biopsy**:
        - Reserved for difficult cases or solitary kidneys.
3. Post-Procedure Care:
    - Monitor for bleeding (haematuria, flank pain, hypotension).
    - Bed rest for 6–24 hours.

Findings:

Microscopic Examination	Examples of Diseases
Light Microscopy	Membranous nephropathy (thickened glomerular capillaries).
Immunofluorescence	IgA nephropathy (mesangial IgA deposits).
Electron Microscopy	Minimal change disease (podocyte effacement).

Complications:

1. **Bleeding**:
    - Haematuria (common, usually resolves).
    - Perinephric haematoma (rare, severe cases may require intervention).
2. **Infection**:
    - Rare, but requires monitoring.
3. **Arteriovenous Fistula**:
    - Asymptomatic in most cases; rarely requires intervention.
4. **Pain**:
    - Localised to the biopsy site or flank.

Haematuria

Definition

- **Haematuria** is the presence of red blood cells (RBCs) in the urine. It can be **visible** (macroscopic) or **non-visible** (microscopic).

Types of Haematuria

1. **Macroscopic haematuria**: Visible blood in the urine.
2. **Microscopic haematuria**: Detected only on urinalysis or microscopy, with >3 RBCs per high-power field.

Causes

- **Pre-renal (systemic causes)**:
    - Bleeding disorders (e.g., anticoagulant use, coagulopathies)
    - Sickle cell disease
    - Vasculitis

- **Renal (intrinsic kidney causes)**:
  - Glomerulonephritis (e.g., IgA nephropathy, post-streptococcal glomerulonephritis)
  - Polycystic kidney disease
  - Pyelonephritis
  - Renal cell carcinoma
  - Trauma (e.g., kidney injury)
- **Post-renal (lower urinary tract causes)**:
  - Urolithiasis (kidney stones)
  - Urinary tract infection (UTI)
  - Bladder cancer
  - Benign prostatic hyperplasia (BPH)
  - Trauma or catheterisation

Risk Factors

- Age > 50 years
- Smoking (increases risk of urological cancers)
- Family history of kidney disease or malignancy
- Recent upper respiratory infection (may suggest IgA nephropathy)

Clinical Features

- **Macroscopic haematuria**: Bright red or cola-coloured urine.
- **Non-visible haematuria**: Detected on dipstick or urine microscopy.
- **Associated symptoms**:
  - Dysuria, frequency, urgency (UTI or bladder stone)
  - Loin pain (suggesting renal stones or pyelonephritis)
  - Weight loss, fatigue, and night sweats (suggest malignancy)
  - Hypertension and proteinuria (suggesting glomerular cause)

Investigations

1. **Urinalysis**: Confirms haematuria, detects proteinuria and casts.
2. **Urine microscopy**: Determines the number of RBCs and looks for dysmorphic RBCs, which suggest glomerular disease.
3. **Urine culture**: To rule out infection.
4. **Blood tests**: FBC, U&E, clotting profile, renal function.
5. **Imaging**:
   - **Ultrasound**: First-line imaging to evaluate kidneys and bladder.
   - **CT urography**: More sensitive for detecting stones, tumours, or vascular abnormalities.
   - **Cystoscopy**: Performed if haematuria is persistent or if malignancy is suspected.
6. **Renal biopsy**: Indicated if a glomerular cause is suspected (e.g., nephritic syndrome).

Management

1. **Treat the underlying cause**:
   - **Urinary tract infection**: Antibiotics based on urine culture sensitivity.
   - **Renal stones**: Conservative management or surgical intervention (e.g., lithotripsy or ureteroscopy).
   - **Glomerulonephritis**: Immunosuppressive therapy, corticosteroids, or treatment of underlying infection.
   - **Bladder cancer**: Surgery (e.g., transurethral resection of bladder tumour), chemotherapy, or radiotherapy.
   - **Benign prostatic hyperplasia (BPH)**: Alpha-blockers (e.g., tamsulosin) or 5-alpha-reductase inhibitors (e.g., finasteride).

2. **Symptomatic management**:
    - Ensure adequate hydration.
    - Monitor renal function and blood pressure.

Referral Criteria

- All patients with **macroscopic haematuria**.
- Non-visible haematuria in patients > 50 years or with risk factors for urological malignancies.
- Persistent or recurrent haematuria with no clear cause.

Prognosis

- Depends on the underlying cause. Early detection and treatment of malignancy or glomerular disease improve outcomes.

Key Points

- Haematuria can indicate serious underlying pathology, including infection, stones, glomerulonephritis, or cancer.
- Investigate thoroughly to determine the cause, particularly in older patients and those with risk factors for malignancy.

Proteinuria

Definition

- Proteinuria refers to the abnormal presence of **excess protein** in the urine, usually indicating kidney dysfunction or damage to the glomerular filtration barrier.

Causes and Mechanism

- **Glomerular proteinuria:** Damage to the glomerulus leads to leakage of proteins (e.g., albumin).
    - Seen in nephrotic syndrome, diabetic nephropathy, and glomerulonephritis.
- **Tubular proteinuria:** Impaired reabsorption of filtered proteins in the proximal tubule.
    - Seen in tubular disorders like Fanconi syndrome or acute tubular necrosis (ATN).
- **Overflow proteinuria:** Excess production of low molecular weight proteins, overwhelming the kidney's reabsorption capacity.
    - Seen in multiple myeloma (Bence Jones proteins).
- **Post-renal proteinuria:** Results from infection or bleeding along the urinary tract.
    - Seen in urinary infections or bladder tumours.

Diagnostic Approach

1. Urinalysis:

- **Dipstick test**: Screening tool to detect albuminuria.
    - Results: Trace, 1+, 2+, 3+ (indicating increasing protein levels).
    - False positives: Can occur with concentrated urine, fever, or exercise.

2. Quantitative Protein Measurement:

- **24-hour urine protein collection:** Measures total protein excretion (>3.5 g/day indicates nephrotic range proteinuria).
- **Urine Albumin-Creatinine Ratio (ACR):**
    - Normal: <3 mg/mmol
    - Microalbuminuria: 3–30 mg/mmol
    - Clinical proteinuria: >30 mg/mmol

3. Protein Electrophoresis: Used to differentiate between albumin and non-albumin proteins (important for diagnosing multiple myeloma or amyloidosis).

4. Microscopic Urine Examination: Assess for casts (e.g., red cell casts in glomerulonephritis or hyaline casts in dehydration).
5. Renal Function Tests: Serum creatinine and eGFR to assess kidney function.
6. Imaging: Ultrasound: For structural abnormalities (e.g., polycystic kidney disease, hydronephrosis).
7. Renal biopsy: Indicated if glomerular disease is suspected (e.g., nephrotic syndrome, glomerulonephritis).

Management

1. **Treat underlying cause** (e.g., ACE inhibitors/ARBs for diabetic nephropathy).
2. **ACE inhibitors or ARBs:**
   - Reduce intraglomerular pressure and proteinuria.
   - Dose: E.g., Ramipril 2.5–10 mg/day.
3. **Control blood pressure:** Target BP <130/80 mmHg if proteinuria >1 g/day.
4. **Statins:** For hyperlipidaemia in nephrotic syndrome.
5. **Dietary modification:** Low salt and low protein diet.
6. **Immunosuppression:** For immune-mediated glomerulonephritis (e.g., corticosteroids).

Key Points

- **Proteinuria** can be a sign of early kidney disease and must be evaluated with both qualitative and quantitative tests.
- Persistent proteinuria requires further workup to determine the underlying cause.
- Early diagnosis and appropriate management help prevent progression to **chronic kidney disease (CKD).**

Acute interstitial nephritis (AIN)

Definition

- Acute interstitial nephritis is inflammation of the renal tubulo-interstitium, secondary to a hypersensitivity reaction to drugs.

Epidemiology

- accounts for 25% of drug-induced acute renal failure

Pathophysiology

- The onset of AIN occurs approximately 10-14 days after the initiation of the inciting agent and resolves with removal of the offending drug.
- It is **typically** characterised by **Eosinophilia and Eosinophiluria** with elevated levels of **IgE** in the serum suggesting a **type I hypersensitivity**.
- AIN may also be caused by type IV hypersensitivity with mononuclear interstitial infiltrate on renal biopsy.
- Drug → Hypersensitivity reaction (type IV) within the kidney interstitium → acute kidney injury.

Causes

- **Drugs:** the most common cause
  - ⇨ NSAIDs, (the most common cause)
  - ⇨ **Antibiotics:** penicillins, cephalosporins, rifampin, sulfonamides, quinolones, **rifampicin**
  - ⇨ Diuretics: furosemide and thiazides
  - ⇨ Proton pump inhibitors (PPIs)

- ⇨ 5-aminosalicylates (eg, mesalamine)
- ⇨ Allopurinol
- ⇨ Phenytoin
- **Infection:** (eg, *Mycoplasma*)
- **Autoimmune diseases** (eg, Sjögren syndrome, SLE, sarcoidosis).

Features

- **Allergic reaction: triad of rash, fever, and eosinophilia (only 10%)**
- hypertension
- Proteinuria is dominant

Investigations

- **Eosinophilia is common**
- Urine: white cells, red cells, and white cell casts (**Eosinophiluria**)
- Acute Kidney injury (AKI): ↑ creatinine
- **Renal biopsy**: for definite diagnosis → shows mononuclear cell infiltration throughout the interstitium with associated oedema.

Treatment

- **The majority of patients recover following withdrawal of the offending drug**
- High-dose prednisolone is indicated in some cases to hasten recovery.
  - ⇨ NSAID-induced AIN does not generally respond to glucocorticoid therapy.
- Dialysis may be required in severe cases.

Prognosis

- Good prognosis if it is managed early. Untreated AIN results in interstitial fibrosis.

Drug-induced acute interstitial nephritis (AIN)

Remember these 7 P'S:

1. **Pee drugs (diuretics):** Thiazides and furosemide
2. **Pain-free (NSAIDs)**
3. **Penicillins and cephalosporins**
4. **Proton pump inhibitors**
5. **Phenytoin**
6. **RifamPin**
7. **SulPha drugs:** Sulfasalazine, Sulfonylureas

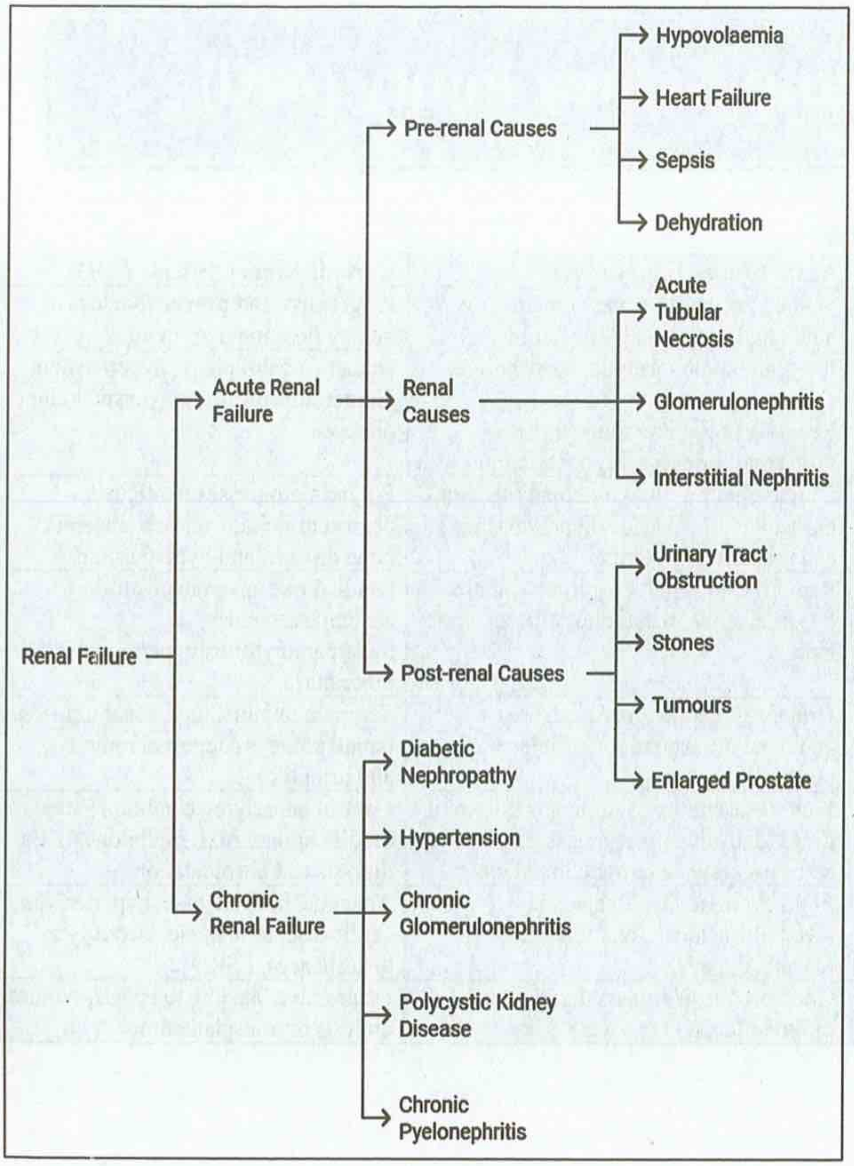
Patients with non-oliguric acute renal failure should always be investigated for **Acute interstitial nephritis (AIN).**

AIN should be suspected in a patient who presents with an elevated serum creatinine and a urinalysis that shows white cells, white cell casts, and, in some cases, eosinophiluria.

Acute Kidney Injury (AKI)

Renal failure

Aspect	Acute Kidney Injury (AKI)	Chronic Kidney Disease (CKD)
Definition	Sudden decline in kidney function over hours to days, typically reversible.	Progressive and irreversible loss of kidney function over months to years.
Causes	Pre-renal: hypovolaemia, heart failure, sepsis. Renal: ATN, glomerulonephritis. Post-renal: urinary tract obstruction.	Diabetic nephropathy, hypertension, glomerulonephritis, polycystic kidney disease.
Clinical Features	Oliguria/anuria, fluid overload (oedema), electrolyte imbalances (hyperkalaemia), and uraemia symptoms.	Polyuria progresses to oliguria, persistent fatigue, nausea, anaemia, bone disease, and hypertension.
Laboratory Findings	Rapid rise in serum creatinine and urea, hyperkalaemia, metabolic acidosis, urine casts.	Gradual rise in serum creatinine, anaemia, secondary hyperparathyroidism, persistent proteinuria.
Diagnosis	Urinalysis, serum creatinine, urea, and renal ultrasound to exclude obstruction.	Serum creatinine, urea, renal ultrasound (small kidneys suggest chronicity), and urinalysis.
Management	Fluid resuscitation, stopping nephrotoxic drugs, dialysis for severe cases, and correcting electrolyte imbalances.	Control underlying conditions, dietary modifications, ACE inhibitors/ARBs, dialysis or transplantation.
Complications	Fluid overload, hyperkalaemia, metabolic acidosis, and uraemia (encephalopathy).	Anaemia, bone disease, hypertension, cardiovascular disease, electrolyte disturbances, ESRD.
Prognosis	Good prognosis if treated early, may progress to CKD in severe cases.	Progressive, leading to ESRD, requires dialysis or transplantation.



Renal Failure
Acute Renal Failure
Chronic Renal Failure
Pre-renal Causes
Renal Causes
Post-renal Causes
Hypovolaemia
Heart Failure
Sepsis
Dehydration
Acute Tubular Necrosis
Glomerulonephritis
Interstitial Nephritis
Urinary Tract Obstruction
Stones
Tumours
Enlarged Prostate
Diabetic Nephropathy
Hypertension
Chronic Glomerulonephritis
Polycystic Kidney Disease
Chronic Pyelonephritis

Acute Kidney Injury (AKI)

Definition

A sudden decline in kidney function, impairing waste elimination, fluid, and electrolyte balance over hours to days.

Causes and Diagnostic Features

Cause	Examples	Diagnostic Features
Pre-renal (Reduced Perfusion)	Hypovolemia (dehydration, hemorrhage) Hypotension (sepsis, shock) Renal artery stenosis Medications (NSAIDs, ACE inhibitors)	- History of hypotension or fluid loss - **Serum urea-to-creatinine ratio >20:1** - **Urine sodium <20 mEq/L**, low urine output - **Fractional excretion of sodium (FENa) <1%**
Intrinsic Renal (Direct Kidney Damage)	Acute tubular necrosis (ATN) Glomerulonephritis Acute interstitial nephritis (AIN) Rhabdomyolysis	- ATN: **Muddy brown casts** in urine, **FENa >2%** - AIN: **Eosinophils** in urine, recent drug exposure - Glomerulonephritis: **Proteinuria, haematuria**, RBC casts - Rhabdomyolysis: **Elevated CK**, myoglobinuria
Post-renal (Obstruction)	Kidney stones Prostate enlargement Urethral strictures	- **Ultrasound or CT**: Hydronephrosis or bladder distension - **Post-void residual volume >100 mL** - Anuria or intermittent urine flow

Diagnostic Criteria (KDIGO Guidelines)

- **Serum Creatinine Rise**
  - ≥0.3 mg/dL (26.5 µmol/L) within 48 hours
  - Or ≥1.5x baseline within 7 days
- **Urine Output** <0.5 mL/kg/hour for >6 hours

Complications

- **Electrolyte Imbalance**: Hyperkalaemia, hyponatraemia, metabolic acidosis
- **Fluid Overload**: Pulmonary oedema, hypertension
- **Uraemia**: Encephalopathy, pericarditis
- **Infection**: Sepsis risk
- **Progression to CKD**: Severe or prolonged AKI can lead to CKD

Management

1. **General Management**
   - Treat the underlying cause
   - **Fluid Management**
     - **Hypovolaemia**: IV crystalloids (e.g., **0.9% saline**)
     - **Hypervolaemia**: **Furosemide 40–80 mg IV**
   - Monitor: Electrolytes, urine output, serum creatinine

2. **Hyperkalaemia Management**
    - **Calcium gluconate 10% IV** (10–20 mL) to stabilize myocardium
    - **Insulin (10 units IV) + glucose (50 mL of 50% dextrose)** to shift potassium intracellularly
    - **Sodium bicarbonate IV** for acidosis
    - **Nebulised salbutamol** (beta-agonist)
    - **Sodium polystyrene sulfonate** for potassium removal
3. **Dialysis indications**
    - Persistent hyperkalaemia
    - Severe acidosis (pH <7.1)
    - Volume overload unresponsive to diuretics
    - Uraemic complications (encephalopathy, pericarditis)
4. **Medications**
    - Stop nephrotoxic drugs (e.g., NSAIDs, ACE inhibitors)
    - **Antibiotics** if infection present (adjust dose for renal function)
    - **Omeprazole 20 mg daily** to prevent stress ulcers

Acute tubular necrosis (ATN)

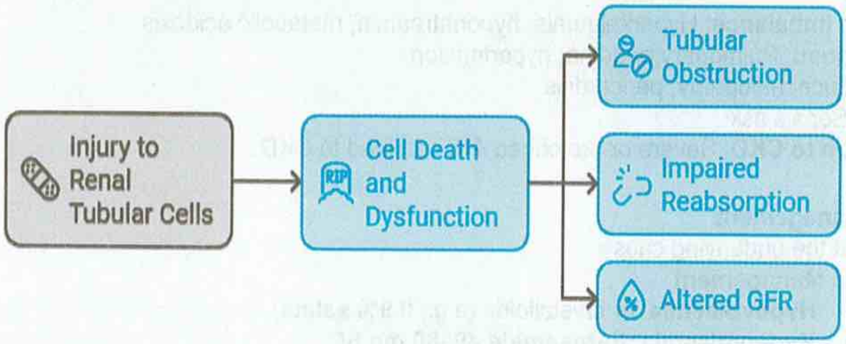
Definition

- **Acute Tubular Necrosis (ATN)** is a type of acute kidney injury (AKI) characterised by the death of tubular epithelial cells within the renal tubules, leading to acute kidney dysfunction. It is usually reversible if detected early and treated appropriately.

Causes

1. **Ischaemic ATN** (due to prolonged hypoperfusion):
    - Severe hypotension or shock (e.g., sepsis, haemorrhage)
    - Cardiovascular collapse (e.g., cardiac arrest, heart failure)
    - Major surgery (especially cardiac or abdominal surgeries)
    - Trauma
2. **Nephrotoxic ATN** (due to toxic damage to the renal tubules):
    - Medications (e.g., aminoglycosides, NSAIDs, amphotericin B, contrast agents)
    - Endogenous toxins (e.g., myoglobin in rhabdomyolysis, haemoglobin in haemolysis, uric acid in tumour lysis syndrome)
    - Exogenous toxins (e.g., heavy metals, ethylene glycol)

Pathophysiology



Clinical Features

1. **Early (Initiation Phase)**:
   - Oliguria (reduced urine output < 400 mL/day) or anuria
   - Symptoms of the underlying cause (e.g., hypotension, sepsis)
2. **Established (Maintenance Phase)**:
   - Persistent oliguria or non-oliguric AKI
   - Rising serum creatinine and urea levels
   - Electrolyte abnormalities (e.g., hyperkalaemia, hyperphosphataemia, metabolic acidosis)
   - Symptoms of fluid overload (e.g., oedema, pulmonary congestion)
3. **Recovery Phase**:
   - Gradual recovery of urine output
   - Resolution of electrolyte abnormalities
   - Gradual decline in serum creatinine and urea levels

Diagnosis

1. **Urine Studies**:
   - **Urinalysis**: Muddy brown casts or epithelial cell casts are suggestive of ATN.
   - **Urine sodium**: Often >40 mEq/L (indicating inability of kidneys to concentrate urine).
   - **Urine osmolality**: Low (<350 mOsm/kg), indicating loss of tubular function.
   - **Fractional excretion of sodium (FENa)**: >2%, suggesting tubular damage.
2. **Blood Tests**:
   - Rising **serum creatinine** and **urea** (indicative of worsening renal function).
   - **Electrolyte disturbances**: Hyperkalaemia, hyperphosphataemia, and metabolic acidosis.
3. **Imaging**:
   - **Renal ultrasound**: Excludes post-renal causes (e.g., obstruction).
   - **CT or MRI**: May be needed in complex cases but usually not essential for diagnosis.

Management

1. **Supportive Care**:
   - **Correct underlying cause**: Restore adequate perfusion in ischaemic ATN (e.g., fluids, vasopressors for hypotension or shock).
   - **Stop nephrotoxic drugs**: Discontinue offending agents (e.g., aminoglycosides, contrast agents).
   - **Fluid management**: Administer intravenous fluids cautiously to prevent fluid overload but maintain renal perfusion.
2. **Electrolyte and Acid-Base Balance**:
   - **Hyperkalaemia**: Treat with calcium gluconate, insulin with glucose, and potassium binders.
   - **Metabolic acidosis**: May require bicarbonate therapy if severe.
   - **Diuretics**: Used in cases of volume overload, but should be avoided in hypovolaemic patients.
3. **Renal Replacement Therapy (RRT)**:
   - **Indications for dialysis**: Refractory hyperkalaemia, severe acidosis, fluid overload unresponsive to diuretics, uraemia.
   - **Types**: Haemodialysis or continuous renal replacement therapy (CRRT) in critically ill patients.

Prognosis

- **Recovery**: Most patients recover renal function if the underlying cause is treated promptly.
- **Chronic kidney disease**: Risk of progression to CKD if the ATN episode is severe or prolonged.
- **Mortality**: Associated with the underlying condition (e.g., sepsis, multi-organ failure).

Comparison Between Acute Tubular Necrosis (ATN) and Acute Interstitial Nephritis (AIN)

Feature	Acute Tubular Necrosis (ATN)	Acute Interstitial Nephritis (AIN)
Definition	Intrinsic renal injury due to tubular cell damage.	Renal injury caused by inflammation of the interstitium and tubules.
Causes	Ischaemia (e.g., shock, sepsis), nephrotoxins (e.g., aminoglycosides, radiocontrast).	Drug-induced (e.g., NSAIDs, antibiotics), infections, or autoimmune diseases.
Pathophysiology	Tubular necrosis leads to obstruction and impaired filtration.	Interstitial inflammation causes oedema and impairs kidney function.
Urine Output	Oliguria to normal.	Often oliguria but can vary.
Urine Findings	Granular "muddy brown" casts, tubular epithelial cells.	Eosinophils, white blood cell casts.
Serum Creatinine	Rises gradually over days.	Rises after exposure to offending agent.
BUN/Creatinine Ratio	Typically < 15:1.	Normal or mildly elevated.
Response to Fluids	Minimal improvement.	May improve if dehydration is a cause.
Management	Supportive care, treat underlying cause, dialysis if needed.	Stop offending drug, steroids in severe cases.
Prognosis	Recovery over weeks to months; chronic injury possible.	Usually reversible if treated promptly.

Comparison Between Acute Tubular Necrosis (ATN) and Prerenal Uraemia

Feature	Acute Tubular Necrosis (ATN)	Prerenal Uraemia
Definition	Intrinsic renal injury due to tubular cell damage.	Decreased renal perfusion without intrinsic kidney damage.
Causes	Ischaemia, nephrotoxins (e.g., aminoglycosides, contrast).	Hypovolemia (e.g., dehydration, haemorrhage), heart failure, or shock.
Pathophysiology	Tubular cells die and slough off, causing obstruction and impaired filtration.	Reduced renal perfusion → decreased glomerular filtration rate (GFR).
Urine Output	May be normal, oliguria, or anuria.	Oliguria (low urine output).
Urine Sodium (mEq/L)	>40 (due to tubular dysfunction).	<20 (kidney retains sodium to increase perfusion).
Urine Osmolality (mOsm/kg)	<350 (inability to concentrate urine).	>500 (concentrated urine).

Feature	Acute Tubular Necrosis (ATN)	Prerenal Uraemia
BUN/Creatinine Ratio	<15:1 (normal ratio).	>20:1 (due to increased urea reabsorption).
Urinalysis Findings	Granular ("muddy brown") casts tubular epithelial cells.	Bland urine (no casts).
Response to Fluid Resuscitation	Minimal improvement.	Rapid improvement with fluids.
Serum Creatinine	Steady rise over days.	Rapid improvement with restored perfusion.
Management	Supportive care, manage underlying cause, possible dialysis.	Fluid resuscitation and correction of underlying cause (e.g., treat dehydration).
Prognosis	Recovery in weeks to months, possible chronic kidney injury.	Rapid recovery with prompt treatment.

Differences between Papillary Necrosis and Acute Tubular Necrosis (ATN)

Aspect	Acute Tubular Necrosis (ATN)	Papillary Necrosis
Definition	Damage to renal tubular epithelial cells, leading to impaired kidney function.	Necrosis of renal papillae due to ischemia or toxic injury.
Causes	- Ischemia (e.g., hypotension, shock) - Nephrotoxic agents (e.g., aminoglycosides, contrast media) - Sepsis	- Pyelonephritis - Obstruction - Sickle cell disease - NSAID overuse - Diabetes mellitus
Clinical Features	- Oliguria or anuria - Muddy brown casts in urine - Elevated creatinine - Hyperkalaemia	- Flank pain - Haematuria - Dysuria - Possible fever with infection
Diagnosis	- Urinalysis: Granular casts, epithelial cells - Blood tests: Increased creatinine and BUN - FENa >2%	- Imaging (CT or IVU): Sloughed papillae or ring shadows - Urine analysis: RBCs, WBCs, necrotic tissue
Complications	- Chronic kidney disease - Electrolyte imbalance (e.g., hyperkalaemia) - Metabolic acidosis	- Ureteric obstruction - Pyelonephritis - Chronic kidney disease
Treatment	- Fluid resuscitation - Discontinue nephrotoxic drugs - Dialysis if needed for severe cases	- Treat underlying cause (e.g., antibiotics for infection) - Relieve obstruction if present - Stop offending drugs
Prognosis	Good with early management, but severe cases can lead to chronic renal impairment.	Depends on early intervention; may progress to chronic kidney disease if untreated.

Contrast-induced acute kidney injury (CI- AKI)

Definition

- A **25% increase in creatinine** within 3 days of intravenous (IV) contrast exposure (e.g., during angiography).

Risk Factors

- **Chronic kidney disease** (eGFR < 40 mL/min/1.73 m²)
- **Heart failure** or hypotension
- Age ≥ 75 years
- **Hypovolemia** or dehydration
- Increasing volume of contrast agent

Prevention

- **Adequate hydration** with NaCl before and after contrast administration (the most important preventive step).
- Temporarily stop **ACE inhibitors and ARBs** if eGFR < 40 mL/min/1.73 m².
- **Metformin:**
  - **Contraindicated** if eGFR < 30 mL/min/1.73 m² (↑ risk of lactic acidosis).
  - **No need to stop** if eGFR ≥ 30 mL/min/1.73 m² before or after contrast use.

Comparison of Iodinated Contrast vs Gadolinium Contrast

Feature	Iodinated Contrast	Gadolinium Contrast
Usage	Primarily for **CT scans**	Primarily for **MRI studies**
Safety in Kidney Function	Safe if **eGFR ≥ 30 mL/min/1.73 m²** and in **anuric patients on chronic haemodialysis**	Safer than iodinated contrast (less nephrotoxic) but can cause **nephrogenic systemic fibrosis (NSF)** in severe renal impairment
Nephrotoxicity	**Higher nephrotoxicity** risk	**Lower nephrotoxicity** risk
Risk of Allergic Reactions	Higher likelihood of **allergic reactions**	Lower likelihood of **allergic reactions**
Complication in Severe Renal Impairment	Can worsen renal function and lead to **contrast-induced nephropathy**	May cause **NSF** (extremely rare but serious complication)
Indications	Used for diagnostic **angiography**, CT chest, abdomen, and pelvis studies	Used for soft tissue evaluation in **MRI** (e.g., brain, joints, liver)
Mechanism of Action	Contains iodine, enhancing **X-ray absorption**	Contains gadolinium, enhancing **magnetic properties** during MRI
Onset of Complications	Immediate or within a few days	NSF may occur **days to years** after exposure
Patient Considerations	**Hydration** recommended to prevent nephropathy	Avoid in patients with **severe renal impairment** (eGFR < 30 mL/min/1.73 m²)

Management (supportive like other AKI)

- Avoid further nephrotoxic causes
- Assess and manage hemodynamic and electrolyte imbalance
- Dose adjustment of medications for the reduction in GFR,
- Monitor for uremic signs and symptoms.
- Dialysis is rarely required (usually mild GFR reduction)

Prognosis: Most patients return to their baseline within 7 days.

Rhabdomyolysis

Definition

- Rhabdomyolysis is the **breakdown of skeletal muscle fibres**, leading to the release of muscle contents, including **myoglobin, potassium, and creatine kinase (CK)**, into the bloodstream.

Causes

- **Trauma**: Crush injuries, prolonged immobilisation.
- **Exercise-induced**: Intense physical exertion (e.g., marathon running).
- **Drugs and toxins**: Statins, fibrates, alcohol, cocaine, heroin.
- **Infections**: Influenza, HIV, bacterial sepsis.
- **Metabolic disorders**: Hypokalemia, hypophosphatemia, hypothermia.
- **Heatstroke**: Severe hyperthermia.
- **Genetic predisposition**: McArdle's disease, malignant hyperthermia.

Pathophysiology

- **Muscle injury or stress** disrupts the muscle cell membrane, causing **cell lysis**.
- Release of **myoglobin** into circulation can lead to **acute kidney injury** (AKI) through tubular obstruction and toxicity.
- **Electrolyte imbalances**: Hyperkalemia, hyperphosphatemia, and hypocalcemia due to muscle content release.

Clinical Features

- **Muscle pain**: Generalised or localised, often in the calves or lower back.
- **Swelling**: Due to muscle damage.
- **Dark-coloured urine**: Due to myoglobinuria (tea or cola colour).
- **Fatigue and weakness**.
- **Systemic signs**: Fever, confusion, nausea.

Complications

- **Acute kidney injury (AKI)**: From myoglobin toxicity and hypovolemia.
- **Electrolyte disturbances**: Hyperkalemia (can cause cardiac arrhythmias), hypocalcemia.
- **Disseminated intravascular coagulation (DIC)**.
- **Compartment syndrome**: Increased pressure within muscle compartments, impairing circulation.

Diagnosis

- **Serum creatine kinase (CK)**: Elevated, often >5 times the upper limit of normal.
- **Myoglobinuria**: Detected by positive dipstick for haemoglobin without red blood cells in urine.
- **Serum electrolytes**: Hyperkalemia, hyperphosphatemia, hypocalcemia.
- **Renal function tests**: Elevated creatinine and urea indicating AKI.
- **Urinalysis**: May show dark urine with no red cells.

Management

Intervention	Details
Fluid resuscitation	Aggressive IV fluids (e.g., normal saline) to maintain urine output >200-300 mL/hour.
Electrolyte correction	Manage hyperkalemia (e.g., IV calcium, insulin with glucose).
Alkalinisation of urine	IV sodium bicarbonate to reduce myoglobin toxicity.
Diuretics (e.g., mannitol)	May be used to promote diuresis.
Dialysis	For severe AKI with electrolyte imbalance unresponsive to treatment.
Treatment of underlying cause	Address trauma, drug overdose, or metabolic disorders.

Collapse + ARF → rhabdomyolysis - treat with IV fluids

Rhabdomyolysis can result from co-prescription of clarithromycin and statins

Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD)

Definition

CKD is characterised by abnormalities in kidney structure or function, persisting for more than three months, with implications for health. Diagnostic criteria include a glomerular filtration rate (GFR) <60 mL/min/1.73 m² or markers of kidney damage (e.g., albuminuria).

Classification

GFR Category	GFR (mL/min/1.73 m²)	Description
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mild to moderate decrease
G3b	30–44	Moderate to severe decrease
G4	15–29	Severe decrease
G5	<15	Kidney failure

Albuminuria Category	Albumin-to-Creatinine Ratio (ACR)	Description
A1	<30 mg/g	Normal to mild
A2	30–300 mg/g	Moderate
A3	>300 mg/g	Severe

Causes

- **Diabetes mellitus** (most common in the U.S. and UK)
- **Hypertension**
- **Glomerulonephritis**
- **Polycystic kidney disease**
- **Obstructive uropathy** (e.g., kidney stones)
- **Autoimmune diseases** (e.g., lupus nephritis)
- **Nephrotoxic drugs** (e.g., NSAIDs, aminoglycosides)

Diagnostic Criteria

- **Symptoms and Signs:**
    - Fatigue, nausea, anorexia
    - Oedema (peripheral, pulmonary, peri-orbital)
    - Hypertension
    - Polyuria and nocturia (early stages)
    - Oliguria or anuria (late stages)
    - Uraemia symptoms: confusion, pruritus, metallic taste, muscle cramps
- **Laboratory Tests and Imaging:**
    - **GFR <60 mL/min/1.73 m²** for ≥3 months
    - **Proteinuria (albuminuria)** (>30 mg/g creatinine)
    - **Elevated creatinine, urea, and potassium**
    - **Electrolyte imbalances:** hyperkalemia, hypocalcemia, hyperphosphatemia
    - **Ultrasound:** small, shrunken kidneys, loss of cortical thickness
    - **Urinalysis:** proteinuria, hematuria
    - **Albumin-to-creatinine ratio (ACR):** >30 mg/g

Complications

- **Cardiovascular disease** (leading cause of death)
- **Hypertension**
- **Anaemia** (reduced erythropoietin)
- **Mineral and Bone Disorder (MBD):** fractures, hypocalcemia
- **Electrolyte disturbances:** hyperkalemia, metabolic acidosis
- **Fluid overload:** pulmonary oedema
- **Progression to end-stage renal disease (ESRD)**

Disorders of Mineral and Bone Metabolism in CKD

Disorder	Mechanism	Diagnosis	Treatment
Hypocalcaemia	- Impaired conversion of vitamin D to active form (**calcitriol**) ↓ intestinal calcium absorption - Hyperphosphatemia causes calcium-phosphate precipitation - Elevated PTH tries to restore calcium.	- **Low serum calcium** - Elevated PTH (secondary hyperparathyroidism) - Low calcitriol levels	- **Calcitriol:** 0.25–0.5 mcg/day - **Calcium carbonate:** 500–1000 mg with meals (if phosphate controlled) - **Cinacalcet:** 30–180 mg/day if PTH remains elevated.
Hyper-phosphataemia (PO_4)	- **Reduced renal excretion of phosphate** - Phosphate retention leads to calcium-phosphate precipitation and hypocalcaemia.	- **Elevated serum phosphate** (>4.5 mg/dL or >1.46 mmol/L) - Check PTH, calcium, and vitamin D levels.	- **Sevelamer:** 800–1600 mg with meals (binds phosphate) - **Calcium carbonate:** 500–1000 mg with meals - **Dietary phosphate restriction.**
Secondary Hyper-parathyroidism	- **Hypocalcaemia** and **hyperphosphatemia** stimulate excess PTH release - Chronic PTH elevation causes **bone resorption** and **renal osteodystrophy.**	- **Elevated PTH** (above normal range) - Low serum calcium - Elevated phosphate	- **Calcitriol:** 0.25–0.5 mcg/day - **Paricalcitol** as an alternative - **Cinacalcet:** 30–180 mg/day (calcimimetic)
Renal Osteodystrophy	- **Secondary hyperparathyroidism** and **impaired calcium/phosphate metabolism** lead to defective bone mineralization.	- Bone pain, fractures - X-rays: signs of osteitis fibrosa cystica - Elevated PTH, low calcium	- **Calcitriol and phosphate binders** - Correct calcium/phosphate levels - **Monitor PTH levels** regularly. - Weight-bearing exercise to improve bone strength.

Disorder	Mechanism	Diagnosis	Treatment
Extra-skeletal Calcification (Metastatic calcification)	- Excess phosphate leads to calcium-phosphate deposition in soft tissues (e.g., **vessels, heart, lungs**).	- **Vascular calcification on imaging** - Increased serum calcium and phosphate - Complications: cardiovascular disease, organ dysfunction	- **Sevelamer:** 800–1600 mg with meals (non-calcium phosphate binder) - Avoid calcium supplements if hypercalcemia - Optimize phosphate and calcium levels. - **Cinacalcet** if hyperparathyroidism persists.

Management

1. **General Measures:**
   - **Blood pressure control:**
     - Target: <130/80 mmHg
     - **ACE inhibitors or ARBs** (e.g., Lisinopril 10–40 mg daily) for proteinuria
   - **Glycaemic control:**
     - Target HbA1c <7%
     - **SGLT2 inhibitors** (e.g., Dapagliflozin) to slow CKD progression
   - **Lipid control:**
     - **Statins** (e.g., Atorvastatin 20–40 mg) for cardiovascular protection
2. **Management of Complications:**
   - **Anaemia:**
     - **Erythropoiesis-stimulating agents (ESAs):** Epoetin alfa 50–150 units/kg subcutaneously 3 times weekly
     - Iron supplements if ferritin <100 ng/mL
   - **Mineral and Bone Disorder (MBD):**
     - **Phosphate binders:** Sevelamer 800–1600 mg with meals
     - **Calcitriol** for secondary hyperparathyroidism
   - **Hyperkalemia:**
     - **Calcium gluconate 10 mL IV** for cardiac protection
     - **Insulin + dextrose:** 10 units IV insulin with 50 mL of 50% dextrose
   - **Fluid overload:**
     - **Loop diuretics** (e.g., Furosemide 40–80 mg daily)
   - **Metabolic acidosis:**
     - **Sodium bicarbonate** if serum bicarbonate <22 mEq/L
3. **Lifestyle Modifications:**
   - Low-sodium diet (<2 g/day)
   - Weight management, exercise, smoking cessation
4. **Renal Replacement Therapy (RRT):**
   - **Indications:** GFR <15 mL/min/1.73 m^2 with symptoms or complications
   - Options: **Haemodialysis, peritoneal dialysis**, or **kidney transplantation** (definitive treatment)

Monitoring

- Regular monitoring of **GFR, albuminuria, electrolytes, haemoglobin, calcium, and phosphate** every 3–6 months
- Monitoring for side effects from ACE inhibitors or ARBs

Diabetic Nephropathy

Section	Notes
Definition	- Diabetic nephropathy is a progressive kidney disease caused by **damage to the glomeruli** due to chronic hyperglycaemia, resulting in proteinuria and declining kidney function.
Pathophysiology	- Chronic hyperglycaemia → **glycation of proteins** and endothelial dysfunction → glomerular damage. - Hyperfiltration → increased intraglomerular pressure → mesangial expansion and thickened glomerular basement membrane. - **Podocyte injury** → protein leakage into urine (albuminuria). - Progressive loss of nephron function → **fibrosis** and **glomerulosclerosis**.
Risk Factors	- **Duration** of diabetes (especially >10 years). - **Poor glycaemic control** (high HbA1c). - **Hypertension**. - Family history of nephropathy. - **Obesity** and smoking. - African or South Asian ethnicity.
Stages	1. **Hyperfiltration stage:** Increased GFR but no proteinuria. 2. **Microalbuminuria (30-300 mg/day):** Early marker of kidney damage. 3. **Macroalbuminuria (>300 mg/day):** Overt proteinuria with declining GFR. 4. **Decline in GFR:** Progression to chronic kidney disease (CKD). 5. **End-stage renal disease (ESRD):** Requires dialysis or transplantation.
Diagnosis	- **Urine Albumin-to-Creatinine Ratio (ACR):** Detects microalbuminuria (>30 mg/g). - **Serum creatinine and eGFR:** Assess kidney function. - **24-hour urine collection:** Quantify proteinuria. - **Blood pressure measurement:** Monitor for hypertension. - **Fundoscopy:** Screen for diabetic retinopathy (common co-manifestation).
Management	1. **Glycaemic control:** - **Target HbA1c** ≤ 7%. - Use insulin or oral antidiabetics (e.g., metformin or GLP-1 receptor agonists). 2. **Blood pressure control:** - **Target BP:** <130/80 mmHg. - Use ACE inhibitors (e.g., **ramipril** 5-10 mg/day) or ARBs (e.g., **losartan** 50-100 mg/day) to reduce proteinuria and protect kidneys. 3. **Lipid management:** - **Statins** to control cholesterol. 4. **Dietary measures:** - Low-sodium and low-protein diet. 5. **Stop smoking and weight management:** Essential lifestyle modifications.

Anaemia in Chronic Kidney Disease (CKD)

Aspect	Details
Mechanism	- **Erythropoietin deficiency**: Damaged kidneys produce insufficient erythropoietin, decreasing red blood cell production. - **Iron deficiency**: Chronic inflammation and blood loss reduce iron availability. - **Uremic toxins**: Impair erythropoiesis and reduce red blood cell lifespan. - **Nutritional deficiencies**: Folate or vitamin B12 deficiency can worsen anaemia.
Diagnostic Criteria	- **Complete Blood Count (CBC)**: Detects reduced haemoglobin and haematocrit. - **Serum Ferritin**: Evaluates iron stores (low levels suggest iron deficiency). - **Transferrin Saturation (TSAT)**: < 20% indicates iron deficiency. - **Reticulocyte Haemoglobin Content (CHr)**: < 29 pg suggests iron-deficient erythropoiesis. - **Serum erythropoietin levels**: Can indicate deficiency.
Management	**1. Correct Iron Deficiency** - **Oral Iron**: For non-dialysis patients (e.g., ferrous sulphate 200 mg, 2-3 times/day). - **IV Iron**: For dialysis patients or those who do not respond to oral iron (e.g., iron sucrose 100-200 mg IV per session). - **Blood transfusion**: In emergencies only (e.g., symptomatic anaemia with unstable haemodynamics). **2. Erythropoiesis-stimulating agents (ESAs)** - **Epoetin alfa**: 50-100 IU/kg subcutaneously or IV 1-3 times weekly. - **Darbepoetin alfa**: 0.45 mcg/kg once weekly or biweekly.
Management Targets	- **Haemoglobin (Hb)**: 10-11.5 g/dL (avoid exceeding 13 g/dL to prevent cardiovascular risks). - **Ferritin**: > 100 µg/L for non-dialysis patients; > 200 µg/L for haemodialysis patients. - **TSAT**: > 20% - **Blood Pressure Monitoring**: Required during ESA therapy to prevent hypertension.

Erythropoietin (EPO)

Aspect	Details
Definition	Erythropoietin (EPO) is a glycoprotein hormone primarily produced by the kidneys. It regulates red blood cell (RBC) production by stimulating erythropoiesis in the bone marrow.
Mechanism of Action	EPO binds to erythropoietin receptors on erythroid progenitor cells in the bone marrow, promoting differentiation into mature RBCs. It also inhibits apoptosis of these progenitor cells.
Physiological Role	- Secreted in response to **hypoxia** (low oxygen levels) - Increases RBC production to enhance oxygen-carrying capacity
Causes of EPO Deficiency	- **Chronic Kidney Disease (CKD)** (most common cause) - **End-stage renal disease (ESRD)** - Chemotherapy-induced bone marrow suppression
Diagnostic Use	- EPO levels can be measured to differentiate between types of anaemia: → **Low EPO levels**: CKD-related anaemia → **High EPO levels**: Compensatory response to chronic hypoxia (e.g., lung disease)
Therapeutic Use	- **CKD-related anaemia**: Given as recombinant erythropoiesis-stimulating agents (ESAs) - **Anaemia due to chemotherapy or bone marrow disorders**
Common Erythropoiesis-Stimulating Agents (ESAs)	- **Epoetin alfa**: 50-100 units/kg 3 times weekly - **Darbepoetin alfa**: Longer half-life; 0.45 mcg/kg once weekly
Side Effects	- Hypertension - Headache - Increased risk of thromboembolism (e.g., stroke, DVT) - Pure red cell aplasia (rare)
Contraindications	- Uncontrolled hypertension - Hypersensitivity to ESAs
Monitoring	- **Target Hb level:** 10-12 g/dL (avoid exceeding 13 g/dL to reduce thrombotic risks) - **Serum ferritin and transferrin saturation (TSAT):** Monitor iron status to ensure effective EPO therapy
Iron Supplementation	- EPO treatment requires adequate iron stores - Target: Ferritin 200-500 µg/L; TSAT >20% - Intravenous iron is preferred for haemodialysis patients

Renal replacement therapy (RRT)

Types of RRT

Type	Description	Indications	Examples
Haemodialysis (HD)	Blood is filtered externally using a dialysis machine.	Chronic kidney disease, acute kidney injury	Hospital-based, home-based dialysis
Peritoneal Dialysis (PD)	Dialysate fluid is introduced into the peritoneal cavity to filter waste.	Suitable for patients with vascular access issues	CAPD (Continuous Ambulatory PD), APD (Automated PD)
Continuous Renal Replacement Therapy (CRRT)	Continuous dialysis for haemodynamically unstable patients.	Critically ill patients in ICU	CVVH (Continuous Venovenous Haemofiltration), CVVHD (Continuous Venovenous Haemodialysis)
Renal Transplantation	Surgical replacement of the kidney with a donor organ.	Suitable patients with ESKD	Live or cadaveric donor

Indications for RRT

1. **Acute Indications (for AKI)** – *AEIOU Criteria*:
   - **A**: Acidosis – Severe metabolic acidosis (pH < 7.2)
   - **E**: Electrolytes – Refractory hyperkalaemia (K+ > 6.5 mmol/L)
   - **I**: Intoxications – Overdose (e.g., lithium, ethylene glycol)
   - **O**: Overload – Pulmonary oedema refractory to diuretics
   - **U**: Uraemia – Symptomatic (e.g., pericarditis, encephalopathy)
2. **Chronic Indications (for CKD)**:
   - eGFR <15 mL/min/1.73m² with symptoms of uraemia
   - Intractable hypertension or fluid overload
   - Malnutrition refractory to medical therapy

Haemodialysis (HD) – Key Points

- **Mechanism**: Blood passes through an external filter, removing toxins and fluid.
- **Frequency**: Typically 3 sessions per week (4-5 hours per session).
- **Vascular Access**:
  - **AV fistula** (preferred)
  - Central venous catheter (temporary use)
- **Complications**:
  - **Hypotension**: Managed with fluids or reducing the ultrafiltration rate.
  - **Cramps**: Treat with saline infusion or quinine sulfate.
  - **Infections**: Prevent with proper catheter care and AV fistula hygiene.

Complications of Hemodialysis (HD)

Complication	Mechanism	Diagnostic Features	Treatment
Hypotension	Fluid removal during dialysis → hypovolemia	Dizziness, syncope, low BP during HD	IV fluids, midodrine (2.5–10 mg orally)
Muscle Cramps	Rapid fluid shifts causing electrolyte imbalance	Painful muscle spasms during HD	Fluid repletion, quinine (300 mg)
Infections (Sepsis)	Contaminated lines/catheters	Fever, chills, local erythema	Antibiotics (IV vancomycin or ceftriaxone)
Dialysis Disequilibrium Syndrome	Rapid osmotic shift → cerebral edema	Nausea, headache, confusion, seizures	Slow dialysis, mannitol
Hyperkalemia	Inadequate dialysis clearance	Muscle weakness, ECG changes	Repeat dialysis, calcium gluconate, insulin with glucose
Anemia	Loss of erythropoietin production and hemolysis	Fatigue, pallor	Erythropoietin (50–100 units/kg 3 times/week) + iron supplementation
Vascular Access Thrombosis	AV fistula or graft blockage	Absent thrill, low dialysis flow	Thrombectomy, alteplase (2 mg)
Air Embolism	Air entering venous lines	Chest pain, dyspnea, hypotension, confusion	Stop dialysis, Trendelenburg position (left lateral decubitus position to trap air in the right atrium),100% oxygen therapy, mechanical ventilation if needed.
Electrolyte Imbalance (Hypocalcemia)	Removal of calcium during dialysis	Tetany, paresthesia	IV calcium gluconate
Pruritus	Uremic toxins or histamine release	Itchy skin	Antihistamines or gabapentin (100–300 mg/day)

Peritoneal Dialysis (PD) – Key Points

- **Mechanism**: Utilises the peritoneal membrane for diffusion of solutes.
- **Advantages**: Home-based, better fluid balance control.
- **Complications**:
  - **Peritonitis**: Common presenting with abdominal pain and cloudy effluent. Treat with intraperitoneal antibiotics.
  - **Catheter blockage**: Manage with saline flushes.
  - **Hernias**: Surgical repair if symptomatic.

Continuous Renal Replacement Therapy (CRRT) – Key Points

- **Mechanism**: Gradual clearance of solutes over 24 hours.
- **Indication**: For haemodynamically unstable patients (ICU setting).
- **Complications**:
  - **Filter clotting**: Managed with anticoagulation (e.g., heparin).
  - **Hypothermia**: Use of a blood warmer.

Renal Transplantation – Key Points

- **Donors**: Live or deceased.
- **Immunosuppression**: Lifelong therapy (e.g., tacrolimus, mycophenolate, steroids).
- **Complications**:
  - **Rejection**: Acute (weeks to months) or chronic (years).
  - **Infections**: Prophylaxis required (e.g., trimethoprim-sulfamethoxazole).
  - **Post-transplant malignancy**: Increased cancer risk due to immunosuppression.

Monitoring and Follow-up

- **Dialysis patients**: Regularly monitor fluid status, electrolytes, and haemoglobin.
- **Post-transplant patients**: Monitor renal function (serum creatinine) and signs of rejection.
- **Infections**: Routine screening for hepatitis B, C, and HIV.

Summary of Drug Use in RRT

Drug	Mechanism	Indications	Dose	Side Effects
Erythropoietin	Stimulates RBC production	Anaemia of CKD	50-100 units/kg, SC, 1-3 times weekly	Hypertension, thrombosis
Cinacalcet	Reduces parathyroid hormone (PTH)	Secondary hyperparathyroidism	30-180 mg daily	Hypocalcaemia
Sevelamer	Phosphate binder	Hyperphosphataemia	800-1600 mg per meal	GI upset
Tacrolimus	Calcineurin inhibitor	Post-transplant immunosuppression	0.1-0.2 mg/kg/day (initial)	Nephrotoxicity, tremors

Graft Rejection Types

Aspect	Hyperacute Rejection	Accelerated Rejection	Acute Cellular Rejection	Chronic Rejection
Definition	Occurs within minutes to hours after transplantation	Occurs within 2-5 days after transplantation	Occurs within days to weeks	Gradual loss of graft function over months to years
Patho-physiology	Pre-formed donor-specific antibodies activate complement → rapid thrombosis and graft necrosis	T-cell and antibody response against donor antigens	T-cell-mediated immune response against donor antigens	Progressive vascular changes, chronic inflammation, and fibrosis
Frequency	Rare (<1%)	Rare (1-5%)	Common (10-30% in the first 3 months)	Most common cause of late graft loss (>50% of long-term failures)

Aspect	Hyperacute Rejection	Accelerated Rejection	Acute Cellular Rejection	Chronic Rejection
Causes & Risk Factors	Pre-existing anti-HLA antibodies, ABO incompatibility	Partial compatibility issues, previous sensitisation	Inadequate immunosuppression, HLA mismatching	HLA mismatching, suboptimal immunosuppression, infection
Diagnostic Features	Immediate graft dysfunction, no urine output, cyanotic or mottled graft	Sudden graft dysfunction, graft swelling, decreased urine output	Increased creatinine, graft tenderness, fever	Slowly rising creatinine, proteinuria, hypertension
Prevention	ABO compatibility, cross-matching	Pre-transplant cross-matching	Close monitoring of immunosuppressive therapy	Strict adherence to immunosuppressive regimen
Treatment	Immediate graft removal	High-dose steroids, anti-thymocyte globulin	High-dose corticosteroids (e.g., methylprednisolone 500–1000 mg IV daily for 3 days)	No definitive treatment, optimise immunosuppression, treat complications.

Graft versus Host Disease (GVHD)

Aspect	Details
Definition	A condition that occurs when transplanted donor immune cells (graft) recognize the recipient's tissues (host) as foreign and attack them. Commonly seen in bone marrow and stem cell transplants.
Types	**Acute GVHD**: Occurs within the first 100 days post-transplant. **Chronic GVHD**: Occurs after 100 days or can persist long-term.
Mechanism	Donor T-cells attack recipient tissues, causing immune-mediated damage to organs.
Common Affected Organs	Skin, liver, gastrointestinal tract, and eyes.
Risk Factors	- HLA mismatch between donor and recipient - Unrelated donor transplant - Older recipient age - Use of peripheral blood stem cells (PBSCT) instead of bone marrow
Diagnostic Features	**Skin**: Maculopapular rash, pruritus. **Liver**: Elevated liver enzymes (alkaline phosphatase, bilirubin). **GI tract**: Diarrhoea, nausea, abdominal pain. **Eyes**: Dry eyes, irritation (in chronic GVHD).
Prevention	- **Immunosuppressive therapy** (e.g., cyclosporine, tacrolimus) started before transplant. - Use of T-cell depletion in donor grafts.

Aspect	Details
Treatment	**Acute GVHD**: - **Corticosteroids** (prednisolone or methylprednisolone 1-2 mg/kg/day). - **Immunosuppressants** (e.g., tacrolimus, cyclosporine). **Chronic GVHD**: - **Corticosteroids** (lower doses). - **Additional immunosuppressants** (mycophenolate mofetil or sirolimus). - Symptomatic treatments for specific organ involvement.
Complications	- Infections due to immunosuppression - Organ dysfunction (liver, lungs) - Increased risk of relapse of the underlying disease

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Definition

- ADPKD is a genetic disorder characterised by the progressive development of multiple fluid-filled cysts in both kidneys, leading to kidney enlargement and eventual renal dysfunction.

Types

Type	ADPKD Type 1	ADPKD Type 2
Prevalence	85% of cases	15% of cases
Chromosome	Chromosome 16	Chromosome 4
Progression	Faster progression; ESRF by 50s	Slower course; ESRF by 70s

Clinical Features

- **Renal symptoms**:
  - Flank pain or abdominal discomfort
  - Haematuria (gross or microscopic)
  - Recurrent urinary tract infections (UTIs) or nephrolithiasis (kidney stones)
  - Hypertension (common and often occurs early)
  - Progressive renal insufficiency, eventually leading to **chronic kidney disease (CKD)**.
- **Extrarenal manifestations**:
  - **Polycystic liver disease** (most common extrarenal manifestation)
  - **Intracranial aneurysms** (risk of subarachnoid haemorrhage)
  - **Mitral valve prolapse** and other valvular disorders
  - **Hernias** (inguinal or abdominal hernias)
  - **Colonic diverticula**

Extra-Renal Manifestations of ADPKD

Manifestation	Description	Frequency
Hypertension	Early onset due to renal artery compression or activation of the renin-angiotensin-aldosterone system (RAAS).	60-80%
Hepatic Cysts	Asymptomatic in most cases but can lead to hepatomegaly and pain. More common and severe in women.	80% (by age 40)
Cerebral Aneurysms	Increased risk of subarachnoid haemorrhage, especially in those with a family history of aneurysms.	5-10%
Mitral Valve Prolapse	Can result in palpitations, fatigue, or heart murmur.	20-25%
Aortic Root Dilation / Aneurysm	Can cause aortic regurgitation and increase the risk of dissection.	5-10%
Diverticulosis	Increased risk of colonic diverticula and complications such as diverticulitis.	10-30%
Abdominal Wall / Inguinal Hernias	Common due to increased intra-abdominal pressure from enlarged kidneys.	40%
Pancreatic Cysts	Usually asymptomatic and benign.	10%
Seminal Vesicle Cysts	Can lead to infertility in men.	40% (in males)
Cardiac Valvular Abnormalities	Mitral valve prolapse (MVP) is commonly found in 25%, often accompanied by tricuspid regurgitation.	20%
Bronchiectasis	Structural lung changes that may lead to recurrent infections.	Rare (<5%)

Diagnosis

Investigation	Findings
Ultrasound	Multiple bilateral renal cysts. Diagnostic criteria: at least 3 cysts in one kidney if <30 years old, and ≥4 cysts in each kidney if >60 years old.
CT/MRI	Provides detailed imaging, used if ultrasound results are inconclusive.
Genetic testing	Useful in cases with unclear family history or in younger patients.

Complications

- **Hypertension**: Occurs due to cyst-induced activation of the renin-angiotensin system.
- **Chronic kidney disease (CKD)**: Progressive loss of renal function.
- **End-stage renal disease (ESRD)**: Usually occurs by the age of 50-70 years in PKD1 mutation cases.
- **Urinary tract infections**: Particularly cyst infections.
- **Nephrolithiasis**: Calcium oxalate stones are common.

Management

Aspect	Details
Blood pressure control	Target BP <130/80 mmHg. **ACE inhibitors** or **ARBs** are first-line agents.
Tolvaptan	Vasopressin receptor antagonist used to slow cyst growth and preserve renal function in patients with rapidly progressing ADPKD. **Dose:** Start with 45 mg in the morning and 15 mg in the evening, titrate based on tolerance.
Pain management	Use analgesics or cyst decompression procedures if needed.
Infection management	Antibiotics for cyst infections, with drugs like **ciprofloxacin** or **trimethoprim-sulfamethoxazole** that penetrate cysts.
Lifestyle modifications	Low-salt diet, adequate hydration, and avoidance of nephrotoxic drugs.
Management of CKD/ESRD	Dialysis or renal transplantation may be required in advanced cases.
Intracranial aneurysms	Screen only if there is a personal/family history of aneurysm or symptoms suggestive of subarachnoid haemorrhage.

Family Screening Recommendations

Aspect	Details
Who Should Be Screened?	First-degree relatives (siblings, children, parents) of affected individuals.
When to Screen?	**Adults:** After the age of 18 to avoid psychological impact. **Children:** Not routinely recommended unless clinically necessary (e.g., hypertension management).
Screening Methods	**Ultrasound:** First-line tool to detect renal cysts. **Diagnostic criteria:** - Age 15–39: ≥ 3 cysts (unilateral or bilateral) - Age 40–59: ≥ 2 cysts in each kidney - Age ≥ 60: ≥ 4 cysts in each kidney **Genetic Testing:** Offered if diagnosis is uncertain, **for subjects who are considering donating a kidney to a relative affected by the disease** or for family planning purposes. **MR angiography:** In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms. **Renal biopsy is contraindicated** due to a high risk of haemorrhage into a cyst

Prognosis

- **PKD1 mutation**: ESRD typically occurs earlier (age 50-60).
- **PKD2 mutation**: ESRD develops later (age 70 or beyond).
- **Tolvaptan** can slow disease progression but requires regular monitoring for liver toxicity.

Comparison Between Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Feature	ADPKD	ARPKD
Inheritance Pattern	Autosomal dominant	Autosomal recessive
Genetic Mutation	**PKD1** (Chromosome 16) or **PKD2** (Chromosome 4)	**PKHD1** (Chromosome 6)
Onset of Symptoms	Adulthood (usually in 30s–50s)	Infancy or early childhood
Incidence	1 in 1,000 live births	1 in 20,000 live births
Kidney Involvement	Bilateral large cysts in cortex and medulla	Multiple small cysts in collecting ducts
Renal Failure	Gradual progression to ESRD by age 50–70	ESRD often develops in childhood or adolescence
Hypertension	Common, develops gradually	Early onset, often in infancy
Extra-renal Manifestations	Liver cysts, intracranial aneurysms, mitral valve prolapse	Congenital hepatic fibrosis, portal hypertension
Liver Involvement	Liver cysts (usually asymptomatic)	Congenital hepatic fibrosis → portal hypertension
Complications	ESRD, aneurysm rupture, cardiovascular issues	Respiratory failure from lung hypoplasia, variceal bleeding
Diagnosis	Ultrasound, genetic testing	Prenatal ultrasound, genetic testing
Management	BP control, dialysis, kidney transplantation	Supportive care, dialysis, kidney or liver transplant
Prognosis	ESRD by mid to late adulthood	Variable; severe cases may cause neonatal death

Alport's syndrome

Definition

- A genetic disorder characterised by progressive kidney disease, hearing loss, and eye abnormalities caused by mutations in the collagen IV gene, which affects the basement membranes of kidneys, cochlea, and eyes.

Pathophysiology

- Mutation in **COL4A3, COL4A4, or COL4A5** genes affecting Type IV collagen.
- Leads to defective glomerular basement membrane, resulting in kidney dysfunction.
- Also affects the cochlea (inner ear) and lens of the eyes.

Genetic Inheritance

- **X-linked inheritance** (most common, ~85%): Mutations in COL4A5.
- **Autosomal recessive**: Mutations in COL4A3 or COL4A4.
- **Autosomal dominant** (rare).

Clinical Features

- **Renal involvement**:
  - Haematuria (persistent or intermittent)
  - Proteinuria
  - Progressive renal dysfunction, leading to **chronic kidney disease** (CKD) and **end-stage renal disease (ESRD)**.
- **Auditory involvement**: **Sensorineural hearing loss** (usually by adolescence).

- **Ocular involvement**:
    - Anterior lenticonus (conical lens) – pathognomonic feature.
    - Corneal abnormalities.
    - Macular flecks.

Diagnosis

- **Urine analysis**: Microscopic or gross haematuria, proteinuria.
- **Kidney biopsy**: Electron microscopy showing **thickened, split, or lamellated glomerular basement membrane.**
- **Genetic testing**: Identification of mutations in COL4A3, COL4A4, or COL4A5.
- **Audiometry**: To detect sensorineural hearing loss.
- **Ophthalmological examination**: For anterior lenticonus or other ocular findings.

Complications

- Progression to **end-stage renal disease (ESRD)** by adulthood (especially in males with X-linked disease).
- **Hearing loss** and visual impairments affecting quality of life.
- Increased risk of vascular disease due to renal impairment.

Management

- **Renal management**:
    - ACE inhibitors or ARBs to slow progression of CKD and reduce proteinuria.
    - **Dialysis or kidney transplant** for ESRD.
- **Hearing aids**: Early use for sensorineural hearing loss.
- **Ophthalmologic interventions**: Regular follow-ups for visual abnormalities.
- **Genetic counselling**: Important for families due to hereditary nature.

Prognosis

- Variable depending on the type of inheritance and severity.
- **X-linked males** have a more severe course, often progressing to ESRD by 30-40 years.
- Kidney transplant can be curative, but patients are at risk for **anti-GBM disease** post-transplant.

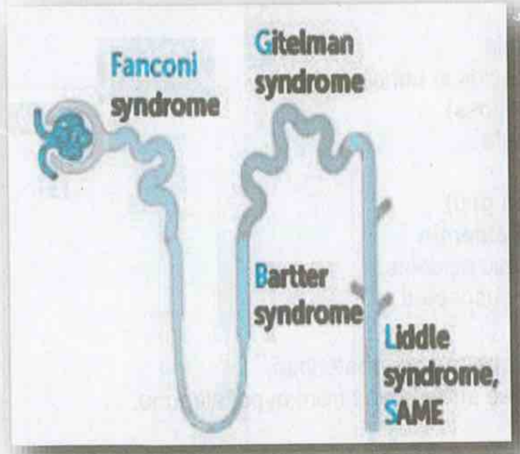
Renal tubular defects

Overview Of Renal Tubular Defects

Disease	Defect/Mechanism	Clinical Features	Diagnosis	Treatment
Fanconi Syndrome	Defect in **proximal tubule** leading to impaired reabsorption of glucose, amino acids, phosphate, and bicarbonate	- Polyuria, polydipsia - Hypo-PO_4 rickets or osteomalacia - Growth retardation - Metabolic acidosis (normal anion gap)	- **Urine:** glucose, amino acids, PO_4 - ↓K acidosis	Treat underlying cause Phosphate and bicarbonate replacement
Bartter Syndrome	Defective **Na-K-2Cl transporter** in the thick ascending loop of Henle	- ↓K, - Polyuria, polydipsia - Growth retardation - Hypercalciuria, nephro-calcinosis	- Urinary electrolyte analysis - Genetic testing	**Potassium supplements**, **NSAIDs** (indomethacin), **ACE inhibitors**
Gitelman Syndrome	Defective **thiazide-sensitive Na-Cl transporter** in the distal convoluted tubule	- Hypo-K - Muscle cramps, fatigue - Tetany - Hypocalciuria, Hypo-Mg	- Urinary magnesium and calcium levels - Genetic testing	**Magnesium** and **potassium supplements** **Spironolactone/ amiloride**
Liddle Syndrome	Mutation causing constitutive activation of **ENaC channel** in the collecting tubule	- Hypertension - ↓K, metabolic alkalosis - No oedema	- ↓K - low aldosterone despite ↑BP	**Amiloride** or **triamterene** (ENaC blockers)

Disease	Defect/Mechanism	Clinical Features	Diagnosis	Treatment
Syndrome of Apparent Mineralocorticoid Excess (SAME)	Deficiency in **11β-hydroxysteroid de-hydrogenase enzyme**, leading to excess activation of mineralocorticoid receptors	- Severe hypertension - ↑K, metabolic alkalosis - Suppressed renin and aldosterone	- **Urine cortisol:** high cortisol-to-cortisone ratio	**Spironolactone** or **eplerenone** **Dexamethasone** (suppresses cortisol)
Type 1 RTA (Distal RTA)	Impaired **hydrogen ion secretion** in the distal tubule	- Metabolic acidosis (normal anion gap) Hypokalaemia - Nephro-calcinosis, kidney stones	- Urine pH > 5.5 - ↓K	**Bicarbonate** and **potassium replacement**
Type 2 RTA (Proximal RTA)	Impaired **bicarbonate reabsorption** in the proximal tubule	- Metabolic acidosis - ↓K - Osteo-malacia/rickets	- Urine pH < 5.5 after bicarbonate therapy	**Bicarbonate supplementation**
Type 4 RTA	**Aldosterone deficiency or resistance,** impairing potassium and hydrogen excretion	- ↑K - Metabolic acidosis	- ↑K - Low renin and aldosterone	**Fludrocortisone** or potassium-binding resins

Locations of renal tubular defects



Fanconi syndrome

Definition

- A disorder of the **proximal renal tubules**, characterised by defective reabsorption of essential substances (e.g., glucose, amino acids, phosphate, bicarbonate) leading to excessive urinary losses.

Pathophysiology

- Impaired **reabsorption in the proximal convoluted tubules** results in the loss of essential solutes.
- This causes **metabolic disturbances** such as hypophosphataemia, metabolic acidosis, and glycosuria despite normal blood glucose levels.

Causes

1. **Genetic (Inherited Autosomal recessive)**:
   - Cystinosis (most common in children)
   - Wilson's disease
   - Glycogen storage diseases (e.g., Type I)
2. **Acquired**:
   - **Drugs**: Ifosfamide, Tenofovir and Aminoglycosides (e.g., gentamicin)
   - **Heavy metals**: Lead, cadmium
   - **Multiple myeloma** (light chain toxicity)
   - **Renal transplantation rejection**
   - **Vitamin D deficiency**

Clinical Features

- **Polyuria** (increased urine output)
- **Polydipsia** (excessive thirst)
- **Dehydration**
- **Rickets or osteomalacia** (bone pain, fractures, poor growth)
- **Metabolic acidosis** (due to bicarbonate loss)
- **Hypophosphataemia** (weakness, muscle pain)
- **Electrolyte imbalances**: Hypokalaemia, hyponatraemia
- **Glycosuria** without hyperglycaemia

Diagnosis

- **Urine tests**:
  - **Glycosuria** without hyperglycaemia.
  - **Aminoaciduria** (elevated amino acids in urine).
  - **Phosphaturia** (excess phosphate loss).
  - **Bicarbonaturia** (loss of bicarbonate).
- **Blood tests**:
  - **Metabolic acidosis** (normal anion gap).
  - **Hypophosphataemia** and **hypokalaemia**.
  - **Elevated urine pH** despite systemic acidosis.
- **Genetic testing**: If inherited causes are suspected.

Complications

- **Bone disease**: Rickets or osteomalacia due to phosphate loss.
- **Electrolyte abnormalities**: Risk of cardiac arrhythmias from hypokalaemia.
- **Growth retardation** in children.
- **Dehydration** and **metabolic acidosis**.

Management

1. **Correction of metabolic abnormalities**:
   - **Oral phosphate supplements** for hypophosphataemia.
   - **Bicarbonate supplementation** for metabolic acidosis.
   - **Potassium supplements** to correct hypokalaemia.
2. **Underlying cause treatment**:
   - Discontinuation of nephrotoxic drugs (e.g., tenofovir, ifosfamide).
   - Management of genetic diseases (e.g., cystinosis with cysteamine).
3. **Supportive measures**:
   - **Vitamin D supplements** to prevent bone disease.
   - **Hydration therapy** to prevent dehydration.
4. **Monitoring**:
   - Regular monitoring of electrolytes and kidney function.
   - Bone density monitoring to prevent fractures.

Prognosis

- Depends on the **underlying cause**.
- **Inherited forms** may require lifelong treatment.
- Early treatment of **acquired causes** can lead to recovery of renal function.

Bartter and Gitelman syndromes

Bartter Syndrome vs Gitelman Syndrome

Feature	Bartter Syndrome	Gitelman Syndrome
Definition	Genetic disorder affecting the **thick ascending limb of the loop of Henle**, impairing sodium, potassium, and chloride reabsorption.	Genetic disorder affecting the **distal convoluted tubule**, leading to impaired sodium and chloride reabsorption.
Genetic Mutation	Mutations in genes like **SLC12A1, KCNJ1, CLCNKB**	Mutations in the **SLC12A3** gene (coding for thiazide-sensitive Na-Cl cotransporter).
Inheritance Pattern	**Autosomal recessive**	**Autosomal recessive**
Prevalence	**Rare (1 in a million)**	**More common (1 in 40,000)**
Age of Onset	Early childhood or neonatal period	Usually presents during adolescence or adulthood
Electrolyte Imbalances	- Hypokalaemia (severe) - Metabolic alkalosis - Hypercalciuria	- Hypokalaemia - Metabolic alkalosis - Hypocalciuria and hypomagnesaemia
Calcium Levels	**Hypercalciuria** → increased urinary calcium	**Hypocalciuria** → decreased urinary calcium
Magnesium Levels	Normal	**Hypomagnesaemia**
Clinical Features	- Polyuria, polydipsia - Muscle weakness, cramps - Growth retardation - Salt craving - Nephrocalcinosis (in severe cases)	- Muscle cramps, weakness - Fatigue - Tetany (due to hypomagnesaemia) - Less severe growth issues

Feature	Bartter Syndrome	Gitelman Syndrome
Blood Pressure	Normal to **low**	Normal to **low**
Urinary Findings	Increased urinary excretion of sodium, potassium, and calcium	Increased urinary excretion of sodium, potassium, and magnesium
Diagnosis	- **Urine electrolytes**: High sodium, potassium, calcium - Genetic testing	- **Urine electrolytes**: High magnesium, sodium, potassium - Genetic testing
Treatment	- **Potassium supplements** - **NSAIDs** (e.g., indomethacin) to reduce renal prostaglandins - **ACE inhibitors** to manage hypercalciuria	- **Magnesium supplements** - **Potassium supplements** - **Spironolactone or amiloride** (potassium-sparing diuretics)
Prognosis	Variable: **Severe forms** may affect growth and renal function	**Better prognosis**, usually responds well to treatment

Key Differences

- **Location of defect**: Bartter (loop of Henle) vs. Gitelman (distal convoluted tubule).
- **Calcium handling**: Bartter (hypercalciuria) vs. Gitelman (hypocalciuria).
- **Magnesium**: Normal in Bartter vs. hypomagnesaemia in Gitelman.
- **Clinical severity**: Bartter is often more severe and diagnosed earlier than Gitelman.

The effects of Gitelman syndrome are similar to those of a thiazide diuretic. The effects of Bartter syndrome are similar to those of a loop diuretic. Loop diuretics work by inhibiting NKCC2. Think of Bartter syndrome as like taking a large dose of furosemide.

Gitelman's syndrome: Normotensive hypokalaemic metabolic alkalosis with Hypocalciuria and significant hypomagnesaemia.

Bartter syndrome: Normotensive hypokalaemic metabolic alkalosis with hypercalciuria, normal or mild hypomagnesaemia, metabolic alkalosis.

The hypokalemia with normal blood pressure in a middle aged male without any skeletal abnormalities or retardation would suggest a diagnosis of Gitelman syndrome rather than Bartter's syndrome.

Liddle's syndrome

Pathophysiology

- **Autosomal dominant** (gain of function mutation) → ↑ **activity of Epithelial Sodium Channels (ENaC)** → ↑ reuptake of water and sodium → Activation of sodium/potassium exchange independent of circulating mineralocorticoid (**pseudohyperaldosteronism**).

Diagnostic features

- Hypertension
- Hypokalaemia
- Metabolic alkalosis
- Decreased renin and aldosterone levels

Treatment

- **Amiloride**: Potassium-sparing diuretics: **acts directly on the sodium channel** → (epithelial sodium channel (ENaC) antagonists). Dose: 50–100 mg orally once or twice daily (MAX: 300 mg per day.)

The clinical features of Liddle syndrome are similar to those of hyperaldosteronism, except that Liddle syndrome manifests with decreased renin and aldosterone levels.

hypokalaemic alkalosis + suppressed renin and aldosterone + hypertension → Liddle's syndrome

Renal tubular acidosis (RTA)

Definition

- Renal tubular acidosis (RTA) refers to a group of disorders characterised by **defective renal acid-base regulation**, resulting in **metabolic acidosis** with normal to near-normal glomerular filtration rate (GFR).

Classification and Pathophysiology

Type	Mechanism	Key Features
Type 1 (Distal RTA)	Inability of distal tubules to excrete H^+ ions	Hypokalaemia, nephrocalcinosis, kidney stones
Type 2 (Proximal RTA)	Impaired bicarbonate reabsorption in proximal tubules	Hypokalaemia, Fanconi syndrome (glycosuria, aminoaciduria, phosphaturia)
Type 4 (Hyperkalaemic RTA)	Reduced aldosterone effect or distal tubular resistance to aldosterone	Hyperkalaemia, mild acidosis, common in diabetic nephropathy

Causes of RTA

- **Type 1**:
  - Autoimmune diseases: **Sjogren's syndrome, lupus**
  - Genetic mutations
  - Amphotericin B toxicity
  - Hypercalciuria, nephrolithiasis
- **Type 2**:
  - **Fanconi syndrome** (e.g., from multiple myeloma, cystinosis)
  - Heavy metal exposure: **lead, cadmium**
  - Carbonic anhydrase inhibitors (e.g., acetazolamide)

- **Type 4**:
    - **Diabetic nephropathy**, chronic interstitial nephritis
    - Drugs: ACE inhibitors, ARBs, spironolactone, NSAIDs
    - Addison's disease (adrenal insufficiency)

Diagnostic Features

- **Blood tests**:
    - Metabolic **acidosis** with **normal anion gap**.
    - Serum **potassium**: Low (Types 1 and 2) or high (Type 4).
- **Urine pH**:
    - **Type 1**: Urine pH > 5.5 (failure to acidify urine).
    - **Type 2**: Variable pH depending on bicarbonate levels.
    - **Type 4**: Urine pH < 5.5 despite hyperkalaemia.
- **Serum bicarbonate**: Low (<22 mEq/L).
- **Urine anion gap (UAG)**: Positive in RTA (helps differentiate from other causes of metabolic acidosis).
- **Electrolytes**: Monitor potassium and bicarbonate levels.

Complications

- **Growth retardation** in children (particularly in Type 1 and Type 2).
- **Nephrocalcinosis** and **kidney stones** (Type 1).
- **Bone demineralisation** (osteomalacia, rickets).
- Chronic **kidney disease (CKD)** if untreated.

Management

- **Type 1 RTA**:
    - **Alkali therapy**: Sodium bicarbonate or potassium citrate (1-2 mEq/kg/day).
    - **Potassium supplements** if hypokalaemic.
- **Type 2 RTA**:
    - **High doses of bicarbonate** or potassium citrate.
    - **Thiazide diuretics** may help reduce bicarbonate loss.
- **Type 4 RTA**:
    - **Fludrocortisone** (mineralocorticoid replacement) if aldosterone deficiency.
    - **Sodium bicarbonate** for acidosis.
    - **Dietary potassium restriction** and use of loop or thiazide diuretics to manage hyperkalaemia.

Prognosis

- Early diagnosis and treatment prevent complications such as growth failure, bone disease, and CKD.
- **Type 4 RTA** may require long-term management, especially in diabetic nephropathy.

Comparison of Types of Renal Tubular Acidosis (RTA)

Feature	Type 1 (Distal RTA)	Type 2 (Proximal RTA)	Type 4 (Hyperkalaemic RTA)
Mechanism	Impaired H^+ secretion in distal tubules	Impaired bicarbonate reabsorption in proximal tubules	Reduced aldosterone effect or resistance in distal tubules
Urine pH	> 5.5 (unable to acidify urine)	Variable (depends on serum bicarbonate)	< 5.5 (despite hyperkalaemia)
Serum Potassium	Low (hypokalaemia)	Low (hypokalaemia)	High (hyperkalaemia)
Associated Conditions	Autoimmune diseases (e.g., Sjogren's, lupus), nephrolithiasis	Fanconi syndrome, heavy metal toxicity (e.g., lead)	Diabetic nephropathy, adrenal insufficiency
Key Features	Nephrocalcinosis, kidney stones, growth retardation	Bone demineralisation, Fanconi syndrome	Hyperkalaemia, mild acidosis
Complications	Kidney stones, osteomalacia, growth failure	Osteomalacia, rickets	CKD, cardiac arrhythmias due to hyperkalaemia
Treatment	Sodium bicarbonate or potassium citrate + potassium supplements	High-dose bicarbonate, potassium citrate + thiazides	Fludrocortisone, sodium bicarbonate, potassium restriction
Prognosis	Good with early treatment	May progress to CKD without management	Long-term management required for CKD

Type 3 Renal Tubular Acidosis (RTA)

Aspect	Details
Definition	Rare condition with combined defects of proximal (Type 2) and distal (Type 1) RTA.
Mechanism	- Impaired **bicarbonate reabsorption** in proximal tubules. - Defective **H^+ excretion** in distal tubules.
Clinical Features	- **Metabolic acidosis**. - **Growth retardation** in children. - **Bone demineralisation** and **rickets**. - May develop **nephrocalcinosis** or kidney stones.
Diagnosis	- **Urine pH:** Varies with serum bicarbonate and acid excretion. - **Serum bicarbonate:** Low. - **Serum potassium:** Normal or low. - Mild proteinuria possible in urinalysis.
Causes	- **Congenital disorders**. - **Inherited enzyme defects** affecting tubule function.
Complications	- **Nephrocalcinosis** and kidney stones. - **Bone diseases** (rickets, osteomalacia). - **Growth failure** if untreated.
Management	- **Bicarbonate therapy:** Corrects acidosis. - **Potassium supplements:** For hypokalaemia. - **Potassium citrate:** Prevents stones and corrects acidosis. - **Thiazide diuretics:** For electrolyte management in severe cases.
Prognosis	Good with early diagnosis and treatment. Untreated cases may lead to **growth retardation** and **chronic kidney disease**.

Syndrome of Apparent Mineralocorticoid Excess (SAME)

Definition and Mechanism

- **SAME** is a rare genetic disorder caused by mutations in the **11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2)** enzyme, leading to an inability to inactivate cortisol to cortisone.
- Cortisol accumulates in the kidneys, mimicking the action of **aldosterone**, resulting in **mineralocorticoid excess** despite low aldosterone levels.

Causes

- **Genetic mutations** affecting 11β-HSD2 enzyme.
- **Exogenous licorice consumption** (glycyrrhizic acid inhibits 11β-HSD2).

Clinical Features

- **Hypertension** (often severe, early onset in childhood).
- **Hypokalaemia** (low potassium levels).
- **Metabolic alkalosis** (due to potassium loss).
- **Suppressed renin and aldosterone levels** (low plasma renin activity).

Diagnosis

- **Low renin and aldosterone levels**.
- **High cortisol:**cortisone ratio in urine (diagnostic marker).
- **Genetic testing** may confirm mutations in the **11β-HSD2** gene.

Complications

- **Cardiovascular risks** (long-term hypertension).
- **Hypokalaemia-induced arrhythmias**.

Management

1. **Mineralocorticoid receptor antagonists**:
   - **Spironolactone** or **eplerenone** to block the effects of cortisol on the kidneys.
2. **Potassium supplementation**:
   - To correct **hypokalaemia**.
3. **Lifestyle adjustments**:
   - **Avoidance of licorice** and substances that inhibit 11β-HSD2.
4. **Low-sodium diet** to manage hypertension.

Prognosis

- With appropriate treatment, **blood pressure** and **electrolytes** can be well controlled. However, **early diagnosis** is essential to prevent cardiovascular complications.

Glomerulonephritides

Glomerulonephritides

Type, Mechanism, and Clinical Presentation

Type of GN	Mechanism	Clinical Presentation
Acute Post-Infectious GN	- Immune complex deposition following infection (e.g., streptococcal) - Activation of complement pathways causing glomerular inflammation	- Hematuria - Proteinuria - Oedema - Hypertension - History of recent infection
IgA Nephropathy (Berger's Disease)	- IgA immune complex deposits in the mesangium - Triggered by mucosal infections (e.g., respiratory or gastrointestinal)	- Recurrent macroscopic hematuria - Gross hematuria following infections - Mild proteinuria
Rapidly Progressive GN (RPGN)	- Crescent formation in glomeruli due to severe glomerular injury - ANCA or anti-GBM antibodies may be involved	- Rapid progression to renal failure - Hematuria with RBC casts - Oliguria - Features of systemic vasculitis in some cases
Membranous GN	- Subepithelial immune complex deposition - Thickening of the glomerular basement membrane	- Nephrotic syndrome: Massive proteinuria, hypoalbuminemia, oedema - Risk of thrombosis
Minimal Change Disease (MCD)	- Loss of podocyte foot processes (effacement) - Mechanism unclear but may involve T-cell dysfunction	- Nephrotic syndrome: Oedema, hypoalbuminemia, hyperlipidemia - Common in children
Focal Segmental Glomerulosclerosis (FSGS)	- Segmental glomerular scarring - Caused by podocyte injury or adaptive response to nephron loss	- Nephrotic syndrome with hematuria - Progressive renal insufficiency - Hypertension
Lupus Nephritis	- Immune complex deposition in glomeruli - Related to systemic lupus erythematosus (SLE)	- Variable presentation: Nephritic or nephrotic syndrome - Haematuria, proteinuria, hypertension - Features of SLE (rash, arthritis, fever)

Type of GN	Mechanism	Clinical Presentation
Anti-GBM Disease (Goodpasture's Syndrome)	- Anti-GBM antibodies attack the glomerular and alveolar basement membranes	- Hemoptysis (lung involvement) - Hematuria and renal failure - Rapid progression to RPGN
Membranoproliferative GN (MPGN)	- Mesangial cell proliferation and thickening of glomerular capillary walls - Immune complex deposition or complement dysregulation	- Mixed nephritic-nephrotic presentation - Hematuria, proteinuria, oedema - Low complement levels (C3, C4)

Diagnosis and Treatment

Type of GN	Diagnostic Features	Treatment
Acute Post-Infectious GN	- Recent infection history (e.g., streptococcal pharyngitis) - Low C3 levels - Urinalysis: Hematuria with RBC casts	- Supportive care - Antibiotics if infection persists - Antihypertensive management
IgA Nephropathy (Berger's Disease)	- Recurrent gross hematuria following infections - Normal complement levels - Renal biopsy: Mesangial IgA deposits	- ACE inhibitors/ARBs to control BP and proteinuria - Corticosteroids for severe cases
Rapidly Progressive GN (RPGN)	- Crescents on renal biopsy - Possible ANCA or anti-GBM antibodies - Urinalysis: Hematuria with RBC casts	- High-dose corticosteroids - Cyclophosphamide - Plasma exchange for severe cases
Membranous GN	- Nephrotic syndrome: Proteinuria, hypoalbuminemia - Renal biopsy: Thickened glomerular basement membrane - Positive anti-PLA2R antibodies	- ACE inhibitors/ARBs - Immunosuppression (e.g., steroids + rituximab) for high-risk cases
Minimal Change Disease (MCD)	- Common in children - Nephrotic syndrome: Severe proteinuria, hypoalbuminemia - Biopsy shows podocyte effacement	- High-dose corticosteroids - Cyclophosphamide for steroid-resistant cases

Type of GN	Diagnostic Features	Treatment
Focal Segmental Glomerulosclerosis (FSGS)	- Nephrotic syndrome with hematuria - Renal biopsy: Segmental glomerular scarring	- ACE inhibitors/ARBs - Steroids + immunosuppressants (e.g., cyclosporine)
Lupus Nephritis	- Associated with systemic lupus erythematosus - Biopsy: Immune complex deposits - Positive ANA and anti-dsDNA	- ACE inhibitors/ARBs - Steroids + mycophenolate or cyclophosphamide
Anti-GBM Disease (Goodpasture's Syndrome)	- Hematuria + hemoptysis - Anti-GBM antibodies in serum - Biopsy: Linear IgG deposits along the GBM	- High-dose corticosteroids + cyclophosphamide - Plasma exchange
Membranoproliferative GN (MPGN)	- Mixed nephritic-nephrotic picture - Low complement levels - Biopsy: Mesangial proliferation and double-contour capillary walls	- ACE inhibitors/ARBs - Steroids + immunosuppressants in severe cases

Diffuse proliferative glomerulonephritis, causes:

- post-streptococcal
- SLE

Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients

Minimal change glomerulonephritis - prednisolone

Nephrotic syndrome in children / young adults - minimal change glomerulonephritis

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

Membranoproliferative glomerulonephritis (mesangiocapillary)
- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Rapidly progressive glomerulonephritis, causes:
- Goodpasture's
- ANCA positive vasculitis

Podocytes fusion is seen in minimal change glomerulonephritis but may occasionally be a feature of focal segmental glomerulosclerosis as well. Minimal change however is far more common

Minimal change disease

Definition

- Minimal change disease (MCD) is a common cause of **nephrotic syndrome**, especially in children, characterised by **podocyte effacement** on electron microscopy without significant abnormalities on light microscopy.

Pathophysiology

- **Podocyte damage** leads to **loss of the glomerular filtration barrier**, resulting in **proteinuria**.
- **Immune dysfunction** is suspected, possibly involving T-cell-mediated injury to the podocytes.
- No immune complex deposits are seen, hence termed "minimal change."

Epidemiology

- Most common cause of **nephrotic syndrome in children** (90% of cases).
- Accounts for **10-15% of nephrotic syndrome cases** in adults.

Causes and Associations

- **Idiopathic**: Most common cause.
- **Secondary causes**:
  - **Infections**: Viral infections (e.g., upper respiratory tract infections).
  - **Allergies**: Food or drug allergies.
  - **Medications**: NSAIDs, rifampin, lithium.
  - **Malignancies**: Particularly Hodgkin's lymphoma.
  - **Autoimmune disorders**: Atopy, eczema.

Clinical Features

- **Nephrotic syndrome**:
  - **Massive proteinuria** (>3.5 g/day)
  - **Hypoalbuminemia** (<30 g/L)
  - **Generalised oedema** (periorbital and peripheral)
  - **Hyperlipidaemia**

- **Normal renal function** in most cases.
- **No hematuria** or hypertension typically at presentation.
- Relapses may occur, particularly after infections.

Diagnosis

- **Urinalysis**: Proteinuria, lipiduria (fat bodies in urine).
- **Serum albumin**: Low levels indicating nephrotic syndrome.
- **Kidney biopsy**:
  - **Light microscopy**: Normal glomeruli (hence "minimal change").
  - **Electron microscopy**: Effacement (fusion) of podocyte foot processes.
  - **Immunofluorescence**: Negative for immune complex deposits.

Complications

- **Infections**: Increased risk of bacterial infections (e.g., cellulitis, sepsis).
- **Thrombosis**: Hypercoagulable state due to loss of antithrombin III.
- **Renal failure**: Rare, but can occur in adults.
- **Relapses**: Particularly following infections or with steroid tapering.

Management

- **First-line treatment**:
  - **Prednisolone** (steroid therapy):
    - **Children**: 2 mg/kg/day (up to 60 mg/day) for 4-6 weeks, followed by tapering.
    - **Adults**: 1 mg/kg/day (up to 80 mg/day) for 4-6 weeks, followed by tapering.
- **Supportive therapy**:
  - **ACE inhibitors/ARBs**: Reduce proteinuria and protect renal function.
  - **Diuretics**: Manage oedema (e.g., furosemide).
  - **Statins**: Manage hyperlipidaemia if persistent.
- **Second-line therapies** (for frequent relapses or steroid-resistant cases):
  - **Cyclophosphamide**: 2 mg/kg/day for 8-12 weeks.
  - **Calcineurin inhibitors**: Tacrolimus or cyclosporine.
  - **Rituximab**: For refractory or steroid-dependent cases.

Prognosis

- **Excellent prognosis** in children with response to steroids.
- **Adults** may have a slower response and higher relapse rates.
- Progression to **end-stage renal disease (ESRD)** is rare.

Membranous glomerulonephritis

Definition and Overview

- **Commonest type of glomerulonephritis** in adults and the **third leading cause** of end-stage renal failure (ESRF).
- **Antibody-mediated disease** with immune complexes deposited between the outer aspect of the basement membrane and the podocyte (subepithelial).
- Presents primarily with **nephrotic syndrome** or **proteinuria**.
- **Males** are affected **twice as often** as females, typically occurring in patients **over 40 years**.

Causes

1. **Idiopathic** (primary).
2. **Infections**:
   - Hepatitis B & C, malaria, syphilis, HIV, schistosomiasis, leprosy.

3. **Malignancies** (secondary):
   - Lung, gastric, colon cancer, non-Hodgkin's lymphoma, leukaemia.
   - **10% of cases are associated with malignancy**.
4. **Drugs**:
   - Gold, penicillamine, NSAIDs, captopril, heavy metals (mercury, cadmium).
5. **Autoimmune diseases**:
   - Lupus (class V), rheumatoid arthritis, thyroiditis.
6. **Other causes**:
   - Diabetes mellitus, sickle cell disease.

Renal Biopsy Findings

1. **Light microscopy**: Diffuse thickening of capillary and glomerular basement membrane.
2. **Electron microscopy**: Thickened membrane with **subepithelial deposits** – creating a **"spike and dome"** appearance.
3. **Immunofluorescence**: Presence of **IgG and C3 deposits**.

Complications

- **Renal vein thrombosis** is common.
  - May present with **left-sided varicocele** due to left testicular vein drainage into the renal vein.
- **Progression to ESRF** in some cases.

Prognosis - Rule of Thirds

1. **One-third**: Spontaneous remission.
2. **One-third**: Persistent proteinuria.
3. **One-third**: Progress to ESRF.

Good Prognostic Factors:

- Female sex, younger age, mild proteinuria at diagnosis.

Management

1. **Immunosuppression**:
   - **Corticosteroids alone** are ineffective.
   - Combination of **methylprednisolone + cyclophosphamide** is commonly used.
2. **Blood pressure control**:
   - **ACE inhibitors (e.g., ramipril)** reduce proteinuria and improve hypertension.
3. **Anticoagulation**:
   - Consider anticoagulation to prevent thrombotic complications.
4. **Treatment of secondary causes**:
   - In secondary membranous nephropathy, addressing the underlying condition can resolve the disease.

IgA Nephropathy (Berger's Disease)

Overview

- The **most common cause of glomerulonephritis worldwide.**
- Caused by **mesangial deposition of IgA immune complexes.**
- Overlaps with **Henoch-Schönlein purpura (HSP).**
- Predominantly affects **males** and is typically diagnosed in **young adults aged 20-40.**

Differentiating IgA Nephropathy from Post-Streptococcal Glomerulonephritis (PSGN)

Feature	IgA Nephropathy	Post-Streptococcal GN
Complement Levels	Normal	Low
Main Symptom	Haematuria	Proteinuria (though haematuria can occur)
Timing after Infection	12-24 hours after upper respiratory infection (URTI)	Delayed onset following infection

Clinical Presentation

- **Recurrent episodes of macroscopic haematuria**, often triggered by mucosal infections (e.g., URTI).
- Haematuria typically occurs **within 12-24 hours of infection.**
- **Loin pain**, muscle pain, and fever may accompany the haematuria.
- **Proteinuria** of nephrotic range is rare.
- Most patients have **normal renal function**, though **renal failure** can develop in some cases.

Associated Conditions

- **Alcoholic cirrhosis**: IgA nephropathy is more likely with haematuria and alcohol excess.
- **Coeliac disease / Dermatitis herpetiformis.**
- **Henoch-Schönlein purpura (HSP).**

Diagnosis

- **Renal biopsy** is the **gold standard.**
  - **Histology**: Mesangial hypercellularity.
  - **Immunofluorescence**: Positive for **IgA** and **C3.**

Management

- **No specific treatment** available; **observation** is the most appropriate management for mild disease.
- **Corticosteroids**: Reserved for patients with **hypertension** and rising creatinine.
  - For **nephrotic-range proteinuria (>3 g/day)**: Prescribe an **8-12 week course of prednisolone.**
  - If **proteinuria is <3 g/day**, treat with **ACE inhibitors** (e.g., **Ramipril**) to reduce proteinuria.
- **Immunosuppressants**: Generally not effective.

Prognosis

- **30%** of children experience **spontaneous remission** within 10 years.
- **25%** of patients develop **end-stage renal failure (ESRF)** within 20 years.
- **Good Prognostic Factors:** Frank haematuria.
- **Poor Prognostic Factors:** Male gender, **proteinuria (>2 g/day)**, hypertension, smoking, hyperlipidaemia, and the **ACE genotype DD.**

Post-streptococcal glomerulonephritis

Definition

- PSGN is an immune-mediated glomerular disease occurring after infections by nephritogenic strains of Group A beta-hemolytic Streptococcus.

Pathophysiology

- **Type III hypersensitivity reaction:** Circulating immune complexes (IgG, IgM, and C3) deposit in the glomeruli, leading to inflammation.
- Immune deposits cause activation of the complement system and inflammation of the glomerular capillaries.

Epidemiology

- Predominantly affects **children** aged 5–12 years.
- More common after **pharyngeal** or **skin** infections (e.g., impetigo).

Clinical Features

- **Latent period:** Symptoms typically appear 7–14 days after throat infections or up to 3–6 weeks after skin infections.
- **Nephritic syndrome** features:
    - Haematuria (cola-coloured urine)
    - Oedema (particularly in the face and legs)
    - Hypertension
    - Oliguria or reduced urine output
    - Fatigue, malaise, and fever

Diagnostic Features

- **Serum Complement Levels:** Decreased C3 levels; C4 is usually normal.
- **ASO titre:** Elevated (anti-streptolysin O) confirms recent streptococcal infection.
- **Renal biopsy (rarely needed):**
    - Subepithelial 'humps' visible on electron microscopy.
    - 'Lumpy-bumpy' immunofluorescence due to immune deposits.

Management

- **Supportive care:** Mainstay of treatment.
    - **Fluid and salt restriction:** To control oedema and hypertension.
    - **Antihypertensives:** Loop diuretics (e.g., furosemide) if needed.
    - **Antibiotics:** If active streptococcal infection persists.
- **Monitoring:** Regular follow-up to assess renal function and blood pressure.

Prognosis

- **Children:** 90–95% recover fully without complications.
- **Adults:** Risk of chronic kidney disease is higher, and complete recovery is less common.

Membrano-proliferative glomerulonephritis (MPGN)

Definition

- MPGN is a pattern of glomerular injury characterised by **mesangial proliferation** and **thickening of the glomerular basement membrane**.
- Also called **mesangiocapillary glomerulonephritis**.

Pathophysiology

- Divided into **two main types** based on immune deposits:
  1. **Immune-complex mediated (Type I MPGN)**: Deposition of immune complexes (e.g., IgG, IgM, and C3) in the glomeruli.
  2. **Complement-mediated (Type II/DDD – Dense Deposit Disease)**: Due to uncontrolled activation of the alternative complement pathway (C3 deposition).

Causes

- **Primary MPGN**: Idiopathic, no underlying cause.
- **Secondary MPGN**: Associated with:
  - **Infections**: Hepatitis B, Hepatitis C, endocarditis
  - **Autoimmune disorders**: Systemic lupus erythematosus (SLE)
  - **Malignancies**: Lymphoma, multiple myeloma
  - **Cryoglobulinaemia**

Clinical Features

- **Nephritic syndrome**: Haematuria, hypertension, and mild proteinuria.
- **Nephrotic syndrome**: Heavy proteinuria, hypoalbuminaemia, and oedema.
- **Mixed nephritic-nephrotic presentation.**
- Symptoms may develop gradually over time.
- Renal insufficiency may progress to chronic kidney disease (CKD).

Diagnosis

- **Urine Analysis**:
  - Haematuria and proteinuria.
  - Possible red cell casts.
- **Serology**:
  - Low complement levels (C3).
  - Screen for infections (e.g., Hepatitis B/C).
  - Cryoglobulin levels and autoimmune markers.
- **Renal Biopsy**:
  - **Light microscopy**: Mesangial cell proliferation, thickened basement membrane.
  - **Immunofluorescence**: IgG, C3, and sometimes IgM deposits (Type I MPGN).
  - **Electron microscopy**: Subendothelial immune deposits in Type I; dense intramembranous deposits in Type II (DDD).

Management

- **Primary MPGN**:
  - **Immunosuppressive therapy**:
    - **Corticosteroids**: Prednisolone 1 mg/kg/day.
    - **Rituximab** or **cyclophosphamide** for severe cases.
  - **ACE inhibitors or ARBs**: Reduce proteinuria and control blood pressure.
- **Secondary MPGN**:
  - **Treat underlying cause**: Antiviral therapy for hepatitis, immunosuppression for autoimmune diseases.
  - **Plasma exchange**: For cases with cryoglobulinaemia.**Complications**

- **Progression to CKD.**
- **End-stage renal failure (ESRF)** requiring renal replacement therapy.
- **Thromboembolic events** due to nephrotic syndrome.
- **Recurrent MPGN** in kidney transplants.

Prognosis

- Variable: Depends on the underlying cause and response to treatment.
- **Poor prognosis**: Persistent nephrotic syndrome, severe proteinuria, or rapid progression to CKD.

Comparison between Type I and Type II Membrano-Proliferative Glomerulonephritis (MPGN)

Feature	Type I MPGN	Type II MPGN (Dense Deposit Disease - DDD)
Pathophysiology	Immune-complex mediated, with deposition of IgG, IgM, and C3.	Complement-mediated with abnormal activation of the alternative complement pathway (C3 deposits only).
Location of Deposits	**Subendothelial deposits** between endothelial cells and basement membrane.	**Intramembranous dense deposits** within the basement membrane.
Immunofluorescence Findings	Positive for IgG, IgM, and C3.	Positive only for C3. IgG and IgM usually absent.
Associated Conditions	- Hepatitis B and C - Autoimmune diseases (SLE) - Cryoglobulinaemia - Endocarditis	- Genetic complement pathway mutations - Acquired C3 nephritic factor (C3NeF)
Complement Levels	Low **C3 and C4** due to immune complex formation.	Low **C3**, normal **C4** due to alternative pathway activation.
Light Microscopy Findings	Mesangial hypercellularity with **capillary loop thickening**.	Mesangial proliferation with thickened glomerular basement membrane (GBM).
Electron Microscopy Findings	**Subendothelial deposits** along the GBM.	**Dense intramembranous deposits** within the GBM, giving it a ribbon-like appearance.
Presentation	- **Mixed nephritic-nephrotic syndrome** - Haematuria - Mild proteinuria - Hypertension	- **Nephrotic syndrome** more common - Proteinuria - May have haematuria but less prominent.
Prognosis	Relatively better prognosis; slow progression to CKD.	Worse prognosis with higher risk of **end-stage renal failure (ESRF)**.
Management	- **Corticosteroids** and **immunosuppressive agents** (cyclophosphamide or rituximab). - ACE inhibitors or ARBs to reduce proteinuria.	- No definitive immunosuppressive treatment. - Complement inhibitors are under investigation (e.g., eculizumab). - ACE inhibitors or ARBs for blood pressure control.

Rapidly Progressive Glomerulonephritis (RPGN)

Definition

- RPGN is a **syndrome of rapidly deteriorating renal function**, with a significant decline in the glomerular filtration rate (GFR) over days to weeks, often leading to **acute renal failure**.
- It is characterized by **crescent formation** in glomeruli on renal biopsy.

Pathophysiology and Types

1. **Type I RPGN (Anti-GBM Disease)**
   - **Mechanism**: Autoantibodies target the **glomerular basement membrane (GBM)**.
   - **Example**: Goodpasture's syndrome (involves both kidneys and lungs).
   - **Key Feature**: Presence of anti-GBM antibodies.
2. **Type II RPGN (Immune Complex-Mediated)**
   - **Mechanism**: Caused by **immune complex deposition** in the glomeruli.
   - **Examples**: Post-infectious GN, lupus nephritis, IgA nephropathy, Henoch-Schönlein purpura.
   - **Key Feature**: Positive immunofluorescence for IgG, IgA, IgM, and/or C3.
3. **Type III RPGN (Pauci-Immune)**
   - **Mechanism**: **ANCA-associated vasculitis**, with little or no immune complex deposition.
   - **Examples**: Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA).
   - **Key Feature**: Positive ANCA (c-ANCA or p-ANCA).

Clinical Features

- **General symptoms**: Fatigue, malaise, fever.
- **Renal symptoms**: Oliguria, haematuria, and proteinuria (nephritic syndrome).
- **Systemic signs** (depending on the cause):
  - Pulmonary haemorrhage (Goodpasture's).
  - Skin purpura (vasculitis-related RPGN).
  - Joint pain and rashes (systemic lupus erythematosus).

Diagnosis

1. **Blood Tests**:
   - **Anti-GBM antibodies** (Type I RPGN).
   - **ANCA antibodies** (Type III RPGN).
   - **Complement levels**: Low in immune complex-mediated RPGN (Type II).
2. **Urine Tests**:
   - Haematuria, proteinuria.
   - Red blood cell casts.
3. **Renal Biopsy**:
   - Crescent formation in more than 50% of glomeruli.
   - Immunofluorescence to determine the type (linear deposits for Type I, granular deposits for Type II, negative for Type III).

Management

- **General Measures**:
  - **High-dose corticosteroids** (e.g., methylprednisolone 500–1000 mg IV for 3 days, followed by oral prednisone).
  - **Plasma exchange** for Goodpasture's syndrome and severe ANCA-associated vasculitis.

- **Supportive care**: Control of blood pressure, electrolyte management, and dialysis if needed.
- **Specific Treatment**:

1. **Anti-GBM Disease (Type I)**:
   - **Plasma exchange** to remove circulating antibodies.
   - **Cyclophosphamide** to suppress the immune response.
2. **Immune Complex-Mediated (Type II)**:
   - Treat underlying cause (e.g., lupus nephritis with immunosuppressants like **mycophenolate** or **cyclophosphamide**).
3. **ANCA-Associated Vasculitis (Type III)**:
   - **Rituximab** or **cyclophosphamide** with corticosteroids.
   - **Plasma exchange** if severe lung or kidney involvement.

Focal segmental glomerulosclerosis (FSGS)

Definition

- **FSGS** is a type of glomerular disease characterized by **scarring (sclerosis)** in some glomeruli (focal) and only a portion of the affected glomeruli (segmental).
- It commonly leads to **proteinuria** and **nephrotic syndrome** and is a significant cause of **end-stage renal disease (ESRD)**.

Pathophysiology

- **Podocyte injury and dysfunction** are central to FSGS development.
- **Segmental sclerosis** occurs due to maladaptive responses to injury in glomeruli, leading to scarring.
- Causes include **idiopathic (primary FSGS)** and **secondary FSGS** due to various underlying conditions.

Types and Causes

Type	Description	Examples
Primary (Idiopathic)	No identifiable cause, often severe	Likely related to circulating permeability factors
Secondary	Results from known triggers	HIV infection, heroin use, obesity, sickle cell disease
Genetic	Caused by gene mutations	Podocin and nephrin gene mutations
Adaptive	Results from hyperfiltration	Reflux nephropathy, reduced nephron number
Virus-Associated	Triggered by viral infections	HIV, parvovirus B19

Clinical Presentation

- **Nephrotic syndrome**:
  - Proteinuria (>3.5 g/day)
  - Hypoalbuminaemia
  - Oedema (peripheral and periorbital)
  - Hyperlipidaemia
- **Hypertension** and **haematuria** may also occur.
- **Progressive decline** in renal function if untreated, often leading to CKD or ESRD.

Diagnosis

1. **Urine Tests**:
    - **Proteinuria** (>3.5 g/day).
    - Microscopic **haematuria** in some cases.
2. **Blood Tests**:
    - Hypoalbuminaemia and hyperlipidaemia (nephrotic syndrome).
    - Serum creatinine may be elevated if kidney function is impaired.
3. **Renal Biopsy**:
    - **Light Microscopy**: Focal and segmental glomerular sclerosis.
    - **Immunofluorescence**: Negative or minimal IgM and C3 deposits.
    - **Electron Microscopy**: Diffuse podocyte foot process effacement.

Management

Treatment Option	Description and Dose
Corticosteroids	**Prednisolone**: 1 mg/kg/day (up to 80 mg daily)
Immunosuppressants	**Calcineurin inhibitors (e.g., tacrolimus)**: Used for steroid-resistant cases
ACE inhibitors / ARBs	**Ramipril**: 2.5–10 mg daily (reduce proteinuria and blood pressure)
Statins	Control hyperlipidaemia
Diuretics	Control oedema (e.g., furosemide 40–80 mg/day)
Anticoagulation	Consider in severe nephrotic syndrome to prevent thromboembolism

Complications

- **Progression to ESRD** requiring dialysis or transplantation.
- **Thromboembolism** due to hypercoagulable state.
- **Relapse after treatment** is common, especially in idiopathic FSGS.
- **Recurrence after kidney transplantation** in up to 30% of cases.

Prognosis

- **Variable prognosis** depending on the type and response to treatment:
    - **Primary FSGS**: Poor prognosis, often progresses to ESRD.
    - **Secondary FSGS**: Better prognosis if the underlying cause is treated.

Goodpasture's syndrome

Definition

- **Goodpasture's syndrome** is a **rare autoimmune disorder** characterised by **autoantibodies targeting the glomerular and alveolar basement membranes**, leading to **glomerulonephritis** and **pulmonary haemorrhage**.

Pathophysiology

- Caused by **anti-glomerular basement membrane (anti-GBM) antibodies** directed against the **α3 chain of type IV collagen** in the basement membranes of kidneys and lungs.
- Results in **complement activation**, **inflammation**, and **damage** to the glomeruli and pulmonary capillaries.
- Triggers include:
    - **Infections**

- Smoking
- Exposure to hydrocarbons
- Viral respiratory infections

Clinical Presentation

- **Pulmonary Symptoms**:
  - Haemoptysis (coughing up blood)
  - Shortness of breath (dyspnoea)
  - Pulmonary infiltrates on chest imaging
- **Renal Symptoms**:
  - Haematuria (blood in urine)
  - Proteinuria (mild to moderate)
  - Rapidly progressive glomerulonephritis (RPGN)
  - Oliguria or anuria in severe cases
- **Systemic Symptoms**:
  - Fatigue, malaise, and weight loss.

Diagnosis

1. **Blood Tests**:
   - **Anti-GBM antibodies**: Positive in most cases.
   - **Serum creatinine**: Elevated if renal involvement is severe.
   - **ANCA antibodies**: Can be present (particularly p-ANCA).
2. **Urine Tests**:
   - Haematuria and proteinuria (indicative of glomerular injury).
3. **Imaging**:
   - **Chest X-ray**: Pulmonary infiltrates.
   - **CT scan**: Diffuse alveolar haemorrhage.
4. **Renal Biopsy**:
   - **Linear IgG deposition** along the glomerular basement membrane on immunofluorescence.
   - Crescents may be visible in glomeruli, indicating RPGN.

Management

Treatment	Description and Dose
Plasma exchange (plasmapheresis)	Removes circulating anti-GBM antibodies. Daily sessions for 2–3 weeks.
Corticosteroids	**Methylprednisolone** 1g IV daily for 3 days, followed by oral **prednisolone** 1 mg/kg/day.
Immunosuppressants	**Cyclophosphamide**: 2 mg/kg/day to prevent antibody production.
Supportive care	Oxygen therapy, fluid management, and dialysis if needed.

Complications

- **Acute renal failure**: Often leads to ESRD requiring dialysis or transplantation.
- **Pulmonary haemorrhage**: Can be life-threatening if not treated promptly.
- **Relapse**: Occurs in some cases despite treatment.

Prognosis

- **Prognosis depends on early diagnosis and treatment.**
- Without treatment, **renal failure** and **respiratory failure** are common.
- **Long-term dialysis** or **kidney transplantation** may be required in severe renal cases.

Goodpasture's syndrome
- IgG deposits on renal biopsy
- anti-GBM antibodies

In the acute setting, treatment is focused on:
1. managing life threatening complications of renal failure, such as hyperkalaemia → haemodialysis.
2. Removing the circulating auto-antibody responsible for disease → **plasmapharesis** (therapeutic plasma exchange),
   - **the most important management step in the next few days after haemodialysis**

Nephrotic syndrome

Definition

- A clinical syndrome characterised by **massive proteinuria** (>3.5 g/day), **hypoalbuminaemia**, **oedema**, **hyperlipidaemia**, and **lipiduria**.

Pathophysiology

- Damage to the **glomerular filtration barrier** (podocytes, basement membrane) → increased permeability → **protein loss in urine** → hypoalbuminaemia and reduced oncotic pressure → fluid shift to interstitial space causing oedema. Compensatory **hyperlipidaemia** occurs due to increased lipoprotein production by the liver.

Causes

- **Primary Glomerular Diseases**:
  - Minimal Change Disease (most common in children)
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Membranous Nephropathy
- **Secondary Causes**:
  - **Infections**: Hepatitis B/C, HIV
  - **Systemic diseases**: Diabetes mellitus, Systemic Lupus Erythematosus (SLE)
  - **Drugs**: NSAIDs, Penicillamine
  - **Malignancies**: Lymphomas

Clinical Features

- **General Oedema**: Most prominent in the face, especially around the eyes.
- **Proteinuria**: >3.5 g/day
- **Hypoalbuminaemia**: Serum albumin <30 g/L
- **Hyperlipidaemia**: Elevated LDL, VLDL, and triglycerides
- **Lipiduria**: Presence of fat bodies or "Maltese crosses" in the urine.
- **Other Symptoms**: Frothy urine, fatigue, weight gain from fluid retention.

Diagnostic Features

- **Urinalysis**: Proteinuria, lipiduria, microscopic haematuria may be present.
- **Serum Albumin**: <30 g/L.
- **Lipid Profile**: Elevated cholesterol and triglycerides.
- **Renal Biopsy**: Indicated in adults or steroid-resistant cases to identify the underlying glomerular disease.

Complications

- **Thrombosis**: Due to loss of antithrombin III and increased fibrinogen.
- **Infections**: Due to loss of immunoglobulins in the urine.
- **Acute Kidney Injury (AKI)**: From hypovolaemia or sepsis.
- **Hyperlipidaemia**: Increases the risk of atherosclerosis.
- **Chronic Kidney Disease (CKD)**: From persistent proteinuria and glomerular damage.

Management

Treatment	Description
Corticosteroids	**Prednisolone** 1 mg/kg/day – used for Minimal Change Disease (MCD).
Immunosuppressants	**Cyclophosphamide** or **Tacrolimus** in steroid-resistant cases.
ACE inhibitors / ARBs	Reduce proteinuria by lowering intraglomerular pressure.
Diuretics	**Furosemide** for oedema management; monitor electrolytes.
Statins	For hyperlipidaemia management if persistent.
Anticoagulants	Consider in high-risk cases for thrombosis prevention.
Salt and Fluid Restriction	Helps manage oedema.
Infections	Vaccination against pneumococcus and influenza recommended.

Prognosis

- **Minimal Change Disease**: Good response to steroids.
- **FSGS or Membranous Nephropathy**: Higher risk of progression to CKD.
- **Relapse**: Common in children; requires careful long-term follow-up.

Nephrotic syndrome → Proteinuria (> 3g/24hr) causing → Hypoalbuminaemia (< 30g/L) and Oedema

Lupus Nephritis

Definition

- Lupus nephritis (LN) is an immune-mediated kidney disease associated with **systemic lupus erythematosus (SLE)**, characterized by inflammation and damage to glomeruli due to immune complex deposition.

Pathophysiology

- Deposition of **autoimmune complexes** (IgG, IgA, and C3) in the glomeruli triggers inflammation.
- Can affect any part of the nephron, including glomeruli, tubules, and blood vessels.
- Leads to a **type III hypersensitivity reaction** causing structural damage to the kidneys.

Classification

- **Class I**: Minimal mesangial LN
- **Class II**: Mesangial proliferative LN
- **Class III**: Focal LN (involves <50% of glomeruli)
- **Class IV**: Diffuse LN (involves ≥50% of glomeruli)
- **Class V**: Membranous LN
- **Class VI**: Advanced sclerosing LN (end-stage kidney disease)

Risk Factors

- **Female predominance** (common in reproductive years)
- African-American, Hispanic, and Asian ethnicities have a higher risk of severe disease.

Clinical Features

- **General symptoms**: Fatigue, fever, joint pain, and signs of systemic lupus.
- **Renal symptoms**:
  - **Proteinuria**
  - **Haematuria**
  - **Hypertension**
  - **Oedema** (peripheral and facial)
  - **Acute kidney injury (AKI)** or chronic kidney disease (CKD)
  - **Nephrotic or nephritic syndrome**

Diagnostic Criteria

- **Urinalysis**:
  - Proteinuria, haematuria, and cellular casts.
- **Serum creatinine/GFR**: Assess kidney function.
- **Autoantibodies**:
  - **Anti-dsDNA** antibodies (high specificity for SLE)
  - **Low complement (C3/C4)** levels.
- **Renal biopsy**: Gold standard to classify the type and severity of lupus nephritis.

Complications

- Chronic kidney disease (CKD) and **end-stage renal disease (ESRD)**
- Hypertension
- Thrombotic events (linked with nephrotic syndrome)
- Infections due to immunosuppression

Management

Induction Therapy (Active Disease)

- **Class III/IV LN**:
  - **Mycophenolate mofetil (MMF)**: 2–3 g/day orally.
  - **Cyclophosphamide**: IV pulse therapy (0.5–1 g/m²/month).
  - **Steroids**: Prednisolone (1 mg/kg/day) gradually tapered.
- **Class V LN (Membranous)**:
  - **MMF**: 2–3 g/day or cyclophosphamide.
  - Low-dose steroids may be used.

Maintenance Therapy (After Remission)

- **MMF** or **Azathioprine**:
  - **Azathioprine**: 1–2 mg/kg/day.
- Low-dose steroids if needed.
- **Hydroxychloroquine** (recommended for all SLE patients to reduce flare risk).

Antihypertensive Therapy

- **ACE inhibitors/ARBs**: To control blood pressure and reduce proteinuria.
- Target BP: **<130/80 mmHg**.

Adjunctive Therapy

- **Prophylactic anticoagulation**: In patients with nephrotic syndrome to prevent thromboembolism.
- **Vaccination**: Pneumococcal and influenza vaccines due to immunosuppression.

Prognosis

- **Class III/IV** have the highest risk of progression to **ESRD** if untreated.
- Early diagnosis and aggressive treatment improve outcomes.
- Regular monitoring for disease flares is essential for long-term management.

Renal vascular disease

Definition

- Renal vascular disease refers to conditions that affect the blood vessels of the kidneys, impairing renal perfusion and potentially leading to hypertension, renal ischemia, and kidney failure.

Types and Causes

Type	Cause
Renal artery stenosis (RAS)	Atherosclerosis (older adults), Fibromuscular dysplasia (younger individuals, especially women)
Renal vein thrombosis	Nephrotic syndrome, malignancy, trauma
Atheroembolic renal disease	Cholesterol emboli following vascular procedures
Hypertensive nephropathy	Chronic hypertension causing vascular damage to the kidney
Renal infarction	Thrombosis or embolism causing tissue ischemia
Thrombotic microangiopathy	Associated with hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP)

Clinical Features

- **Hypertension** (especially in renal artery stenosis)
- **Abdominal or flank pain** (renal infarction or vein thrombosis)
- **Oedema** (renal vein thrombosis)
- **Renal dysfunction**: Acute or chronic kidney injury signs
- **Hematuria** or proteinuria

Suspicion for Renal Artery Stenosis (RAS)

- **Refractory hypertension:** Blood pressure >150/90 mmHg despite the use of three different antihypertensives.
- **Recurrent pulmonary oedema:** Occurs despite normal left ventricular function, indicating fluid overload likely from renal dysfunction.
- **Worsening renal function: Serum creatinine rise >20%** or **GFR drop >15%** within 12 months with:
    - High clinical suspicion of widespread atherosclerosis.
    - Decline occurring within the first 2 months of starting an ACE inhibitor or angiotensin receptor blocker (ARB).

Diagnosis

Test	Findings
Doppler ultrasound	Detects abnormal blood flow in renal arteries or veins
CT/MR angiography	Visualises stenosis, thrombus, or infarction
Renal arteriography	Gold standard for diagnosing RAS
Urinalysis	Hematuria, proteinuria (renal vein thrombosis)
Serum creatinine	Elevated in ischemia or infarction

Management

Condition	Treatment
Renal artery stenosis (RAS)	ACE inhibitors or ARBs for blood pressure control; Revascularisation (angioplasty or stenting) in severe cases
Renal vein thrombosis	Anticoagulation (e.g., heparin, warfarin)
Atheroembolic renal disease	Supportive care, statins to stabilise plaques
Renal infarction	Anticoagulation, thrombolysis, or surgery
Hypertensive nephropathy	Strict blood pressure control (ACE inhibitors or ARBs)
Thrombotic microangiopathy	Plasma exchange or eculizumab for HUS/TTP

Complications

- **Chronic kidney disease (CKD)**
- **End-stage renal disease (ESRD)**
- **Uncontrolled hypertension**
- **Pulmonary embolism** (renal vein thrombosis)
- **Heart failure** (due to volume overload from renal dysfunction)

Unilateral renal artery stenosis (RAS) has two common causes:

1. **Atherosclerosis: usually men over the age of 45 years and typically involves the aortic orifice or the proximal 2 cm of the main renal artery.**
2. **Fibromuscular dysplasia: usually women younger than the age of 50 years and typically involves the middle and distal main renal artery or the intrarenal branches.**

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → renal artery stenosis - do MR angiography

A rise in serum creatinine **more than 20% above the baseline** after starting an (ACEI) → hold the drug, monitor renal function and investigate for renal artery stenosis.

Urology and Renal Oncology

Renal stones

Definition

- Renal stones (urolithiasis or nephrolithiasis) are **solid masses** formed from crystals in the kidneys, often composed of calcium, oxalate, or other minerals.

Pathophysiology

- Supersaturation of **minerals** in the urine leads to crystal formation and aggregation into stones. Factors like **urinary pH, urine concentration, and lack of inhibitors** (e.g., citrate) promote stone formation.

Types of Renal Stones

Type	Composition	Risk Factors	Urine pH
Calcium Stones	Calcium oxalate or calcium phosphate	Hypercalciuria, hyperoxaluria, low citrate	Neutral to acidic
Struvite Stones	Magnesium ammonium phosphate	Recurrent UTIs (Proteus, Klebsiella)	Alkaline (>7.0)
Uric Acid Stones	Uric acid	Gout, hyperuricaemia, dehydration	Acidic (<5.5)
Cystine Stones	Cystine	Genetic defect (cystinuria)	Acidic

Risk Factors

- **Dehydration** (most common)
- **High dietary intake** of calcium, oxalate, or protein
- **Family history** of renal stones
- **Recurrent UTIs** (especially with urease-producing bacteria)
- **Hyperparathyroidism**
- **Obesity and metabolic syndrome**

Clinical Features

- **Renal colic**: Severe, intermittent flank pain radiating to the groin.
- **Hematuria**: Microscopic or visible blood in urine.
- **Nausea and vomiting**.
- **Urinary symptoms**: Urgency, frequency, or dysuria if stones are in the ureters or bladder.
- **Infections**: If stones obstruct the urinary tract, leading to pyelonephritis or sepsis.

Diagnosis

Investigation	Findings
Urinalysis	Hematuria, crystalluria, or pyuria
Serum tests	Check for hypercalcaemia, hyperuricaemia
Non-contrast CT scan	Gold standard – detects almost all types
Ultrasound	Useful in pregnancy, but less sensitive
KUB X-ray	Identifies radio-opaque stones (calcium)
Urine culture	Detects infections, especially with struvite stones

Complications

- **Obstruction**: Hydronephrosis and AKI.
- **Infections**: Urosepsis or pyelonephritis.
- **Chronic Kidney Disease**: Recurrent or untreated stones.
- **Renal colic recurrence.**

Management

Treatment	Description
Hydration	Encourage >2.5 L/day urine output to prevent recurrence.
Pain management	**NSAIDs** (e.g., ibuprofen), **opioids** if severe.
Alpha-blockers	**Tamsulosin** (0.4 mg daily) to facilitate stone passage.
Extracorporeal Shock Wave Lithotripsy (ESWL)	Non-invasive stone fragmentation.
Ureteroscopy	Endoscopic removal for ureteral stones.
Percutaneous nephrolithotomy (PCNL)	For large or complex stones (>2 cm).
Prevention	Dietary modification (low sodium, reduced animal protein) and increased fluid intake.
Medications	**Thiazide diuretics** for calcium stones, **allopurinol** for uric acid stones.

Prevention

- **Calcium stones**: Thiazide diuretics, low-oxalate diet.
- **Uric acid stones**: **Allopurinol** (100–300 mg/day) and urine alkalinisation with potassium citrate.
- **Struvite stones**: Treat and prevent infections with antibiotics.
- **Cystine stones**: Maintain high fluid intake and urine alkalinisation.

Prognosis

- Most small stones (<5 mm) pass spontaneously.
- Larger stones often require medical or surgical intervention.
- Recurrence is common, especially without preventive measures.

Renal stones on x-ray

- cystine stones: semi-opaque
- urate + xanthine stones: radio-lucent

Stag-horn calculi

- composed of Struvite (ammonium magnesium phosphate, triple phosphate)
- form in alkaline urine (ammonia producing bacteria such as Ureaplasma urealyticum and Proteus therefore predispose)

Hyperoxaluria

Definition:

Hyperoxaluria is a condition characterized by excessive urinary excretion of oxalate (>40 mg/day in adults), leading to the formation of calcium oxalate crystals, stones, and potentially systemic oxalate deposition.

Types of Hyperoxaluria:

1. Primary Hyperoxaluria (PH):

- **Genetic defect** in hepatic enzymes involved in glyoxylate metabolism.
- Leads to increased endogenous oxalate production.
- **Types**:
  - **PH Type 1**: Deficiency of **alanine-glyoxylate aminotransferase (AGT)**.
  - **PH Type 2**: Deficiency of **glyoxylate reductase/hydroxypyruvate reductase (GRHPR)**.
  - **PH Type 3**: Deficiency of **4-hydroxy-2-oxoglutarate aldolase (HOGA1)**.

2. Secondary Hyperoxaluria:

- Caused by increased dietary oxalate or altered intestinal absorption.
- **Causes**:
  - **Dietary**: High oxalate intake (e.g., spinach, rhubarb, chocolate, tea).
  - **Malabsorptive Disorders**: Crohn's disease, celiac disease, short bowel syndrome.
    - Leads to increased intestinal oxalate absorption.
  - **Exogenous Sources**: Vitamin C (converted to oxalate).

3. Idiopathic Hyperoxaluria:

- No identifiable genetic or secondary cause.

Pathophysiology:

1. **Primary Hyperoxaluria**:
   - Defective glyoxylate metabolism → overproduction of oxalate in the liver.
2. **Secondary Hyperoxaluria**:
   - Increased oxalate absorption in the gut due to fat malabsorption.
   - Free fatty acids bind calcium, reducing its availability to form calcium oxalate in the gut → more oxalate absorbed.
3. **Calcium Oxalate Deposition**:
   - Oxalate combines with calcium to form **calcium oxalate crystals** in urine → nephrolithiasis or nephrocalcinosis.

Clinical Features:

1. **Renal Manifestations**:
   - Recurrent calcium oxalate kidney stones.
   - Nephrocalcinosis (calcium deposition in renal parenchyma).
   - Progressive renal failure (especially in primary hyperoxaluria).
2. **Systemic Oxalosis** (in severe cases):
   - Oxalate deposition in bones, heart, skin, and blood vessels.
   - Pathological fractures, arrhythmias.

Diagnosis:

Laboratory Tests:

- 24-Hour Urine Oxalate:
  - 40 mg/day indicates hyperoxaluria.
- Urine Calcium Oxalate Crystals:
  - Observed on microscopy.
- Plasma Oxalate Levels:
  - Elevated in systemic oxalosis or CKD.

Genetic Testing:

- Confirms primary hyperoxaluria (mutation in **AGXT**, **GRHPR**, or **HOGA1** genes).

Additional Tests:

- Metabolic Workup:
  - Serum calcium, phosphate, parathyroid hormone (rule out hyperparathyroidism).
- Imaging:
  - Ultrasound or CT KUB to detect stones or nephrocalcinosis.

Management:

General Measures:

1. Dietary Modifications:
   - Low oxalate diet (avoid spinach, rhubarb, nuts).
   - Adequate calcium intake (binds oxalate in the gut).
   - Reduce dietary fat in malabsorption conditions.
2. Hydration:
   - Maintain high urine output (>2.5 L/day) to prevent stone formation.

Medical Management:

- Potassium Citrate:
  - Alkali therapy to prevent calcium oxalate precipitation.
- Pyridoxine (Vitamin B6):
  - Used in **PH Type 1** to reduce oxalate production (responsive in AGT deficiency).
- Probiotics (Oxalobacter formigenes):
  - Reduce intestinal oxalate absorption (experimental).

Specific Therapies for Primary Hyperoxaluria:

1. Liver Transplantation:
   - Corrects enzyme defects in PH Type 1.
2. Combined Liver and Kidney Transplant:
   - Indicated in PH with end-stage renal disease (ESRD).

Secondary Hyperoxaluria:

- Treat underlying cause (e.g., manage malabsorption or reduce dietary oxalate).

Complications:

1. **Nephrolithiasis**:
   - Recurrent calcium oxalate stones.
2. **Chronic Kidney Disease (CKD)**:
   - Progression to ESRD.
3. **Systemic Oxalosis**:
   - Life-threatening condition in advanced CKD.

Key Points for MRCP:

1. **Primary Hyperoxaluria** should be suspected in recurrent stone formers with early onset nephrocalcinosis.
2. **Dietary oxalate reduction** and adequate hydration are first-line preventive strategies.
3. **Pyridoxine** is effective in reducing oxalate production in responsive cases of **PH Type 1**.
4. Secondary hyperoxaluria is common in **intestinal malabsorption syndromes**.

Hypercalciuria

Definition:

Hypercalciuria is the excessive excretion of calcium in the urine, typically defined as:

- **Adults**: >4 mg/kg/day (or >250 mg/day for women and >300 mg/day for men).
- **Children**: >4 mg/kg/day.

Types of Hypercalciuria:

1. **Idiopathic Hypercalciuria**:
   - Most common form; no underlying systemic disorder.
   - May be familial.
2. **Secondary Hypercalciuria**:
   - Due to systemic diseases or conditions affecting calcium metabolism.

Pathophysiology: Hypercalciuria arises from disruptions in calcium handling by the kidneys, intestines, and/or bones, leading to:

- Increased intestinal calcium absorption.
- Increased bone resorption.
- Reduced renal calcium reabsorption.

Causes:

1. Idiopathic Hypercalciuria:

- Unknown etiology; often familial.
- Normal serum calcium levels but increased urinary calcium excretion.

2. Secondary Causes:

- **Increased Bone Resorption**:
  - Hyperparathyroidism.
  - Immobilisation.
  - Paget's disease.
- **Increased Calcium Absorption**:
  - Vitamin D intoxication.
  - Granulomatous diseases (e.g., sarcoidosis, tuberculosis).
- **Renal Calcium Leak**:
  - Renal tubular dysfunction.
- **Medications**:
  - Loop diuretics (e.g., furosemide).
  - Glucocorticoids.
- **Other**:
  - Hyperthyroidism.
  - Milk-alkali syndrome.
  - Excessive dietary calcium or sodium intake.

Clinical Features:

1. **Recurrent Kidney Stones**:
   - Calcium oxalate or calcium phosphate stones.
2. **Haematuria**:
   - Microscopic or macroscopic due to stone formation.
3. **Bone Disease**:
   - Osteopenia/osteoporosis due to excessive bone resorption.
4. **Polyuria and Nocturia**:
   - Due to renal dysfunction.

Diagnosis:

Laboratory Tests:

- **24-Hour Urine Calcium**:
  - Gold standard for diagnosis.
  - Adults: >250–300 mg/day.
- **Serum Calcium, Phosphate, PTH**:
  - Differentiate idiopathic hypercalciuria from secondary causes.
- **Serum Vitamin D**:
  - Elevated in vitamin D intoxication.
- **Urine Creatinine**:
  - Ensure accurate 24-hour urine collection.

Imaging:

- **Renal Ultrasound**:
  - Detect nephrocalcinosis or kidney stones.
- **CT KUB**:
  - Identify small or non-obstructive stones.

Management:

General Measures:

1. **Dietary Modifications**:
   - **Adequate Calcium Intake**:
     - Restricting calcium paradoxically increases stone risk.
   - **Reduce Sodium Intake**:
     - Sodium increases calcium excretion.
   - Limit **oxalate-rich foods** (e.g., spinach, rhubarb).
   - Avoid excessive protein intake.
2. **Hydration**:
   - Maintain high fluid intake (>2–3 L/day) to dilute urine.

Pharmacological Treatment:

1. **Thiazide Diuretics**:
   - Decrease urinary calcium excretion by enhancing tubular reabsorption.
   - Examples: Hydrochlorothiazide (12.5–25 mg daily).
2. **Potassium Citrate**:
   - Alkalises urine and reduces calcium oxalate crystallisation.
   - Useful in patients with hypocitraturia.
3. **Bisphosphonates**:
   - Reduce bone resorption in conditions like hyperparathyroidism.
4. **Vitamin D and Calcium Supplementation**:
   - In cases of secondary hypercalciuria due to deficiencies.

Complications:

1. **Nephrolithiasis**:
   - Recurrent calcium stones.
2. **Nephrocalcinosis**:
   - Calcium deposits in the renal parenchyma.
3. **Osteoporosis**:
   - Due to excessive calcium loss from bone.
4. **Chronic Kidney Disease (CKD)**:
   - Secondary to recurrent stones or nephrocalcinosis.

Key Points for MRCP:

1. **Idiopathic hypercalciuria** is the most common cause of recurrent calcium stones.
2. **Thiazide diuretics** are first-line pharmacological treatment to reduce urinary calcium.
3. **Avoid excessive calcium restriction**, as it can increase intestinal oxalate absorption, promoting stone formation.
4. **Evaluate for secondary causes** of hypercalciuria, especially in patients with other systemic symptoms.

Cystinuria

Aspect	Details
Definition	Autosomal recessive disorder causing defective renal tubular reabsorption of cystine.
Pathophysiology	- Mutations in **SLC3A1** or **SLC7A9** impair cystine reabsorption. - Excess urinary cystine precipitates to form stones.
Key Feature	Recurrent **cystine kidney stones** and **hexagonal crystals** in urine.
Age of Onset	Childhood or early adulthood.

Features, diagnosis and management

Clinical Features	Diagnosis	Management
- Recurrent nephrolithiasis. - Renal colic (flank pain). - Microscopic or macroscopic haematuria. - UTI and CKD (complications).	- **Hexagonal cystine crystals** in urine. - **Cyanide-nitroprusside test**: positive (purple colour). - **24-hour urine cystine**: >250 mg/day. - **CT KUB**: radiopaque stones. - **Genetic testing**: SLC3A1 or SLC7A9 mutations.	- **Hydration**: Maintain urine output >3–4 L/day. - **Urine alkalisation**: Sodium bicarbonate or potassium citrate (target pH 7.0–7.5). - **Diet**: Low sodium, reduced protein intake. - **Chelating agents**: D-penicillamine or tiopronin for refractory cases. - **Stone removal**: ESWL, ureteroscopy, or PCNL for large stones.

Complications and prognosis

Complications	Prognosis
- Recurrent kidney stones. - Chronic kidney disease (CKD). - Urinary tract obstruction or infections.	- Lifelong condition requiring regular monitoring and management. - Good prognosis with adherence to hydration and alkalisation therapies.

Comparison of Key Differences Between Cystinuria and Cystinosis

Feature	Cystinuria	Cystinosis
Definition	Defective renal tubular reabsorption of cystine, causing recurrent cystine kidney stones.	Lysosomal storage disorder causing cystine accumulation in tissues due to defective transport.
Genetic Cause	Mutations in **SLC3A1** or **SLC7A9** (renal tubular transporters).	Mutation in **CTNS gene** encoding cystinosin (lysosomal cystine transporter).
Inheritance	Autosomal recessive.	Autosomal recessive.
Primary Issue	Excessive urinary cystine excretion → stone formation.	Intracellular cystine accumulation → multiorgan damage.
Age of Onset	Childhood or early adulthood.	Infancy (nephropathic type) or later in juvenile/adult forms.
Key Symptoms	- Recurrent cystine kidney stones. - Flank pain, haematuria. - No systemic involvement.	- **Proximal tubulopathy (Fanconi syndrome)**: Polyuria, polydipsia. - Growth failure, CKD, systemic cystine deposits.
Systemic Involvement	Absent.	Present (cornea, thyroid, muscle, kidneys, etc.).
Diagnostic Tests	- **Urine microscopy**: Hexagonal crystals. - **Cyanide-nitroprusside test** (positive).	- Elevated **leukocyte cystine levels** (confirmatory). - **Slit lamp**: Corneal cystine crystals.
Management	- High fluid intake (>3–4 L/day). - Urine alkalisation (pH 7.0–7.5). - Chelating agents (D-penicillamine, tiopronin) in refractory cases. - Stone removal if necessary.	- **Cysteamine therapy** (oral and eye drops). - Supportive management for Fanconi syndrome (electrolytes, bicarbonate). - Renal transplantation in ESRD.
Complications	- Recurrent nephrolithiasis. - CKD due to stone damage or obstruction.	- Chronic kidney disease (progression to ESRD). - Multiorgan damage (e.g., eyes, thyroid, muscle).
Prognosis	Good with hydration, alkalisation, and stone management.	Poor if untreated; improved with early cysteamine therapy.

Urinary incontinence (UI)

Definition

- Urinary incontinence refers to the **involuntary leakage of urine** due to a failure in the storage or emptying function of the bladder.

Types and Mechanism

Type	Mechanism	Key Features
Stress incontinence	Weak pelvic floor muscles and urethral sphincter dysfunction	Urine leakage with coughing, sneezing, or physical exertion
Urge incontinence	Overactive bladder (detrusor overactivity)	Sudden, intense urge to urinate followed by leakage
Overflow incontinence	Incomplete bladder emptying (e.g., bladder outlet obstruction or underactive detrusor muscle)	Dribbling of urine, frequent small volumes, nocturia
Functional incontinence	Physical or cognitive impairments prevent timely toilet access	Incontinence unrelated to urinary tract dysfunction
Mixed incontinence	Combination of stress and urge incontinence	Symptoms of both stress and urge incontinence

Causes

- **Stress incontinence**: Childbirth, obesity, prostate surgery, pelvic trauma.
- **Urge incontinence**: Neurological conditions (e.g., stroke, Parkinson's), infections, bladder irritants (caffeine, alcohol).
- **Overflow incontinence**: Diabetes, spinal cord injury, prostatic hypertrophy, medications (e.g., anticholinergics).
- **Functional incontinence**: Mobility issues, dementia, medication side effects.

Risk Factors

- **Age**: Increases with advancing age
- **Gender**: More common in women due to childbirth and menopause
- **Obesity**: Increases intra-abdominal pressure
- **Medications**: Diuretics, sedatives, anticholinergics
- **Neurological diseases**: Parkinson's, multiple sclerosis

Diagnostic Features

- **History**: Assess frequency, volume, and triggers of leakage.
- **Physical examination**: Pelvic exam for women, prostate exam for men.
- **Urinalysis**: Rule out infections or haematuria.
- **Bladder diary**: Document fluid intake, voiding, and leakage over 2–3 days.
- **Post-void residual (PVR) volume**: Identify incomplete bladder emptying.
- **Urodynamic testing**: Evaluate bladder function (for complex cases).

Complications

- **Infections**: Recurrent urinary tract infections (UTIs)
- **Skin irritation**: Dermatitis from prolonged wetness
- **Social isolation**: Due to embarrassment or anxiety
- **Falls**: Nocturia and urgency leading to falls, especially in older adults

Management

Type	Management
Stress incontinence	- **Pelvic floor muscle training (Kegel exercises)** - **Weight loss** - **Duloxetine**: Increases urethral sphincter tone (40 mg twice daily) - **Surgical options**: Mid-urethral sling, bulking agents
Urge incontinence	- **Bladder training** - **Lifestyle changes**: Avoid caffeine, alcohol - **Antimuscarinics**: Oxybutynin (2.5–5 mg 2–3 times/day) or Tolterodine (2–4 mg daily) - **Beta-3 agonist**: Mirabegron (50 mg daily)
Overflow incontinence	- **Catheterisation**: Intermittent or indwelling - **Alpha-blockers**: Tamsulosin (0.4 mg daily) - **Surgery**: Prostatectomy for obstruction
Functional incontinence	- **Address underlying mobility or cognitive issues** - **Scheduled toileting** - **Incontinence products**: Pads, commodes

Prevention

- **Pelvic floor exercises** for women during and after pregnancy
- **Weight management**
- **Limit bladder irritants** (caffeine, alcohol)
- **Manage chronic conditions** (e.g., diabetes, neurological diseases)

Prognosis

- **Variable outcome** depending on the type and underlying cause
- **Stress and urge incontinence** respond well to behavioural and medical treatment
- **Overflow incontinence** may require long-term management strategies like catheterisation or surgery.

Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative

antimuscarinics (e.g. Oxybutynin, Tolterodine) the usual treatment for urge incontinence are contraindicated in patients with a history of urinary retention.

Urinary retention

Types and Mechanism

Type	Mechanism
Acute urinary retention	Sudden inability to urinate, leading to painful bladder distension. May be caused by obstruction, infection, or neurological dysfunction.
Chronic urinary retention	Incomplete bladder emptying over time, often painless. Can result from bladder dysfunction or partial obstruction.

Causes

- **Obstruction**:
  - Benign prostatic hyperplasia (BPH)
  - Urethral strictures
  - Bladder stones
  - Pelvic masses (e.g., tumours)
- **Neurological dysfunction**:
  - Spinal cord injury
  - Multiple sclerosis
  - Parkinson's disease
- **Medications**:
  - Anticholinergics, opioids, alpha-agonists
- **Postoperative**:
  - Due to anaesthesia or prolonged catheter use
- **Infections**: Severe urinary tract infections causing swelling and obstruction

Risk Factors

- **Age**: Common in older adults
- **Gender**: More frequent in men due to prostate enlargement
- **Surgery/anaesthesia**: Temporary bladder dysfunction
- **Medications**: Drugs affecting bladder function
- **Neurological conditions**: Spinal cord injuries, multiple sclerosis

Diagnostic Features

- **Acute urinary retention**:
  - Sudden, painful inability to urinate
  - Distended, palpable bladder
- **Chronic urinary retention**:
  - Frequent urination with small volumes
  - Nocturia, dribbling
  - Incomplete bladder emptying
- **Investigations**:
  - **Post-void residual (PVR)**: Volume >100 mL suggests incomplete emptying
  - **Bladder scan or ultrasound**: Detect bladder distension or residual volume
  - **Urinalysis**: Identify infections or haematuria
  - **Urodynamic studies**: Assess bladder function and outlet obstruction

Complications

- **Infections**: Increased risk of UTIs
- **Bladder stones**: Due to urinary stasis
- **Hydronephrosis**: Backpressure on kidneys
- **Renal failure**: From prolonged obstruction
- **Bladder damage**: Detrusor muscle hypertrophy or atony

Management

Cause	Treatment
Benign prostatic hyperplasia (BPH)	- **Alpha-blockers:** Tamsulosin 0.4 mg daily - **5-alpha reductase inhibitors**: Finasteride 5 mg daily - Surgery: TURP (Transurethral resection of the prostate)
Urethral stricture	- Urethral dilatation or urethroplasty
Neurological dysfunction	- **Intermittent catheterisation** or **indwelling catheter** - **Bethanechol** (for bladder atony) 10–50 mg 3–4 times daily
Infection-related retention	- Treat underlying infection with antibiotics
Postoperative retention	- Temporary catheterisation - Monitor bladder function after removal
Severe acute retention	- **Urgent catheterisation** (urethral or suprapubic)

Benign prostatic hypertrophy (BPH)

Definition

- BPH is a **non-cancerous enlargement of the prostate gland**, leading to urinary symptoms due to **bladder outlet obstruction**.

Pathophysiology

- **Proliferation of prostatic stromal and epithelial cells** results in an enlarged prostate.
- **Androgens** (e.g., dihydrotestosterone) play a role in prostate growth.
- Enlarged prostate obstructs urine flow, causing **bladder hypertrophy** and dysfunction over time.

Risk Factors

- **Age**: Common in men >50 years
- **Family history** of BPH
- **Obesity** and metabolic syndrome
- **Sedentary lifestyle**
- **Diabetes** and cardiovascular diseases

Clinical Features

- **Lower urinary tract symptoms (LUTS)**:
  - **Storage symptoms**: Nocturia, frequency, urgency
  - **Voiding symptoms**: Hesitancy, weak stream, incomplete emptying, straining
  - **Post-void dribbling**
- **Acute urinary retention** in severe cases

Complications

- **Recurrent UTIs** due to incomplete bladder emptying
- **Bladder stones**
- **Hydronephrosis** from backpressure on kidneys
- **Acute urinary retention**
- **Chronic kidney disease** due to prolonged obstruction

Diagnosis

- **History and physical examination**: Digital rectal exam (DRE) for prostate size and texture
- **Urine analysis**: Rule out infection or haematuria

- **Prostate-specific antigen (PSA)**: Elevated in BPH but also in prostate cancer
- **Bladder scan or ultrasound**: Assess post-void residual volume
- **Uroflowmetry**: Measures urine flow rate
- **Cystoscopy**: In cases of recurrent UTIs or suspected obstruction

Management

Treatment Option	Details
Lifestyle changes	Reduce fluid intake before bedtime, avoid caffeine/alcohol, regular physical activity
Medications	**Alpha-blockers**: Relax smooth muscle in prostate and bladder neck (e.g., Tamsulosin 0.4 mg daily) **5-alpha reductase inhibitors**: Shrink prostate size (e.g., Finasteride 5 mg daily)
Combination therapy	Alpha-blocker + 5-alpha reductase inhibitor for moderate to severe symptoms
Anticholinergics	For storage symptoms (urgency, frequency)
Phosphodiesterase-5 inhibitors	Tadalafil 5 mg daily for patients with both BPH and erectile dysfunction
Surgical options	- **TURP (Transurethral Resection of the Prostate)**: Gold standard - **Laser prostatectomy** (HoLEP or PVP): Minimally invasive alternatives

Medications for BPH

	α_1-Blockers	5α-Reductase Inhibitors
Drugs	Prazosin, doxazosin, terazosin, tamsulosin.	Finasteride.
Mechanism	↓ contractility of the prostate and bladder neck.	Block testosterone conversion to the more potent dihydrotestosterone.
Results	Improve symptoms and urinary flow rates; more effective than 5α-reductase inhibitors for symptom relief.	Improve symptoms; ↓ prostate size and PSA, especially in men with larger prostates.
Side effects	**Orthostatic hypotension**, nasal congestion, dizziness, fatigue.	↓ libido, ejaculatory dysfunction, impotence.

Indications for Surgery

- Recurrent urinary retention
- Recurrent UTIs or bladder stones
- Persistent hematuria
- Severe symptoms not responding to medical therapy
- Chronic kidney disease due to bladder outlet obstruction

Prostate cancer

Definition

- **Prostate cancer** is a **malignant growth** originating in the prostate gland, typically **adenocarcinoma.**
- It is often **slow-growing**, with varying clinical behaviour from asymptomatic cases to aggressive forms.

Risk Factors

- **Age**: Common in men >50 years
- **Family history**: Increased risk with family members diagnosed with prostate cancer
- **Ethnicity**: Higher incidence in **African-Caribbean men**
- **Diet**: High intake of red meat, fat, and dairy products
- **Genetic mutations**: BRCA1 and BRCA2 mutations
- **Hormonal factors**: Androgen exposure plays a role in tumour development.

Symptoms and Clinical Features

- **Early stages**: Often asymptomatic, detected through PSA screening
- **Lower urinary tract symptoms (LUTS)**: Frequency, urgency, weak stream, nocturia
- **Advanced disease**:
    - Bone pain (due to metastases, commonly to the spine)
    - Hematuria or blood in semen
    - Weight loss and fatigue
- **Invasion of local structures**: Causes urinary retention or rectal involvement

Diagnosis

- **Prostate-specific antigen (PSA)**: Elevated levels can indicate prostate cancer but can also be raised in BPH or prostatitis
- **Digital rectal examination (DRE)**: Hard, irregular, or nodular prostate
- **Multiparametric MRI (mpMRI)**: Identifies suspicious lesions for biopsy
- **Prostate biopsy**: Confirms diagnosis with Gleason grading of tumour aggressiveness
- **Staging investigations**: CT scan, MRI, or bone scan to detect metastases

Gleason Score and Grading

- **Gleason score**: Sum of the two most prevalent tumour patterns (scored 1–5).
    - **Score ≤6**: Low-grade tumour
    - **Score 7**: Intermediate-grade tumour
    - **Score 8–10**: High-grade tumour

Staging

- **T1**: Tumour not palpable or visible on imaging
- **T2**: Tumour confined to the prostate
- **T3**: Tumour extends beyond the prostate capsule
- **T4**: Tumour invades surrounding tissues

Management

Stage	Treatment Options
Localized (T1–T2)	**Active surveillance**: For low-risk patients **Radical prostatectomy**: Surgical removal **Radiotherapy**: External beam or brachytherapy
Locally advanced (T3)	**Hormone therapy** (androgen deprivation) + radiotherapy
Metastatic (T4)	**Androgen deprivation therapy (ADT)**: Leuprolide (GnRH agonist) or Enzalutamide (anti-androgen) **Chemotherapy**: Docetaxel in advanced cases
Palliative care	For symptom relief in advanced disease (bone pain management with bisphosphonates or radiotherapy)

Complications

- **Urinary incontinence** and **erectile dysfunction** post-surgery or radiotherapy
- **Bone metastases**: Common in advanced disease, causing fractures and pain
- **Hormonal therapy side effects**: Fatigue, hot flashes, osteoporosis

Prognosis

- **5-year survival rate**: High (>98%) for localized disease
- **Prognosis worsens** with metastatic disease but managed effectively with hormone therapy and chemotherapy.

A man of advanced age presenting with bony metastases is most likely to have metastatic prostate cancer.

Renal cell cancer (RCC)

Definition

- Renal cell carcinoma (RCC) is a **malignant tumour** that originates from the epithelial cells of the **renal tubules.**

Epidemiology

- **Accounts for 85%** of primary kidney cancers.
- **Peak incidence:** 60–70 years of age.
- **Male-to-female ratio:** 2:1.

Risk factors

- **Smoking:** Strongest modifiable risk factor.
- **Obesity:** Increases risk, especially in women.
- **Hypertension.**
- **Chronic kidney disease** and dialysis.
- **Genetic disorders:** Von Hippel-Lindau (VHL) syndrome.
- **Family history** of RCC.
- **Occupational exposure:** Cadmium, asbestos.

Pathophysiology

- RCC arises from the **proximal tubule epithelium.**
- Subtypes:
  - **Clear cell RCC** (most common).
  - **Papillary RCC.**
  - **Chromophobe RCC.**
- **Clear cell RCC** is associated with mutations in the **VHL gene**, leading to increased angiogenesis and tumour growth.

Clinical Features

- **Classic triad** (only seen in a minority of cases):
  - **Haematuria** (visible or microscopic).
  - **Flank pain.**
  - **Palpable abdominal mass.**
- **Systemic features:**
  - Weight loss, fever, night sweats, fatigue.
  - **Paraneoplastic syndromes:**
    - Polycythaemia (due to erythropoietin production).
    - Hypercalcaemia.
    - Hypertension.

- **Metastatic features**: Bone pain, cough (lung metastasis).

Diagnosis

1. **Imaging**:
   - **Ultrasound**: Initial investigation for haematuria.
   - **CT scan (abdomen and pelvis)**: Most sensitive test to confirm RCC and assess local invasion and metastasis.
   - **MRI**: Useful for staging and to assess venous invasion.
2. **Lab tests**:
   - **Urinalysis**: Haematuria.
   - **Serum calcium**: Hypercalcaemia.
   - **Complete blood count**: Polycythaemia.
3. **Biopsy**: Generally **avoided** unless the diagnosis is uncertain or for metastatic disease.

Staging

- **T1**: Tumour ≤7 cm, confined to the kidney.
- **T2**: Tumour >7 cm, confined to the kidney.
- **T3**: Tumour invades major veins or adrenal gland but not beyond Gerota's fascia.
- **T4**: Tumour extends beyond Gerota's fascia.

Management

Stage	Treatment Options
Localized RCC (T1-T2)	**Partial nephrectomy** (for smaller tumours) **Radical nephrectomy**: Removal of the kidney for larger tumours
Locally advanced RCC (T3)	**Radical nephrectomy + lymph node dissection** **Adjuvant immunotherapy** (e.g., checkpoint inhibitors)
Metastatic RCC	**Targeted therapy**: Tyrosine kinase inhibitors (e.g., Sunitinib, Pazopanib) **Immune checkpoint inhibitors**: Nivolumab, Pembrolizumab **Cytoreductive nephrectomy** in selected cases
Palliative care	For symptom control in advanced disease (radiotherapy for bone pain)

Complications

- **Metastases**: Common sites include lungs, bones, liver, and brain.
- **Paraneoplastic syndromes**: Hypercalcaemia, polycythaemia, hypertension.
- **Vascular invasion**: Extension into the renal vein or inferior vena cava (IVC).

Prognosis

- **5-year survival rate**:
  - **Localised disease**: >90%.
  - **Locally advanced disease**: 50–70%.
  - **Metastatic disease**: <10%.

Screening Recommendations

- Routine screening is **not recommended** in the general population.
- Screening is reserved for high-risk individuals, such as those with a **family history of RCC** or **genetic predisposition** (e.g., VHL syndrome).

Wilms' Tumour

Aspect	Details
Definition	A malignant kidney tumour (nephroblastoma) primarily affecting children, usually <5 years old.
Epidemiology	- Most common renal tumour in children. - Peak age: 2–3 years. - Slight female predominance.
Genetics	- Associated with mutations in **WT1** or **WT2** genes on chromosome 11. - Syndromes: **WAGR syndrome, Beckwith-Wiedemann syndrome, Denys-Drash syndrome.**
Clinical Features	- **Abdominal mass** (painless, firm, non-tender). - Haematuria (less common). - Hypertension (due to renin secretion). - Fever and weight loss (occasionally).
Diagnosis	- **Ultrasound**: Initial imaging to detect renal mass. - **CT/MRI Abdomen**: Evaluate tumour extent and metastasis. - **Histology**: Required for definitive diagnosis. - **Chest X-ray/CT**: Rule out lung metastases.
Staging (National Wilms' Tumor Study)	- **Stage I**: Confined to kidney, completely resected. - **Stage II**: Extends beyond kidney but completely resected. - **Stage III**: Residual tumour confined to abdomen. - **Stage IV**: Haematogenous metastasis (e.g., lungs, liver). - **Stage V**: Bilateral tumours.
Treatment	- **Nephrectomy**: Surgical removal of tumour (unilateral cases). - **Chemotherapy**: Pre- and/or post-surgery (e.g., vincristine, dactinomycin). - **Radiotherapy**: For advanced stages (Stage III/IV) or metastases. - **Bilateral Disease**: Nephron-sparing surgery where possible.
Prognosis	- Overall 5-year survival >90% with treatment. - Worse prognosis: Anaplastic histology, advanced stage, metastases.
Complications	- Local recurrence or metastasis (e.g., lungs, liver). - Renal failure (in bilateral disease or nephrectomy). - Chemotherapy/radiotherapy side effects (e.g., growth retardation, infertility).

Angiomyolipoma

Definition

- Angiomyolipoma (AML) is a **benign renal tumour** composed of **blood vessels, smooth muscle, and fat tissue**.
- It is the **most common benign tumour** of the kidney.

Epidemiology

- **More common in females** (4:1 female-to-male ratio).
- Often seen in **middle-aged adults**.
- **Association with tuberous sclerosis complex (TSC)**:
  - Up to 80% of patients with TSC have AML.
  - TSC-associated AMLs tend to be **bilateral and multiple**.

Pathophysiology

- AMLs originate from **perivascular epithelioid cells** and contain a mixture of fat, smooth muscle, and thick-walled blood vessels.
- **TSC-associated AMLs** are linked to mutations in **TSC1 or TSC2 genes**, leading to abnormal cell proliferation.

Clinical Features

- **Asymptomatic** in most cases (incidental finding on imaging).
- **Flank pain** or abdominal discomfort in larger lesions.
- **Haematuria** (if tumour ruptures or bleeds).
- **Retroperitoneal haemorrhage** (Wunderlich syndrome) in cases of tumour rupture.
- Large AML (>4 cm) increases the risk of bleeding.

Diagnosis

1. **Imaging**:
   - **Ultrasound**: Hyperechoic mass (due to fat content).
   - **CT scan**: Heterogeneous lesion with areas of **fat density** (diagnostic hallmark).
   - **MRI**: Useful to differentiate from malignant tumours; AMLs show hyperintense signals due to fat.
2. **Laboratory tests**:
   - **Normal renal function** in most cases unless large tumour causes obstruction or haemorrhage.
   - **Urinalysis**: May show haematuria.

Management

Treatment Options	Indications
Observation	Small, asymptomatic AMLs (<4 cm)
Embolization	Symptomatic or growing AMLs; used to control bleeding
Nephron-sparing surgery (partial nephrectomy)	For larger AMLs (>4 cm) or risk of rupture
Radical nephrectomy	If suspicion of malignancy or uncontrolled bleeding
mTOR inhibitors (e.g., everolimus)	For TSC-associated AMLs or inoperable cases

Complications

- **Haemorrhage**: Risk increases with tumour size (>4 cm).
- **Wunderlich syndrome**: Spontaneous rupture leading to retroperitoneal haemorrhage.
- **Renal impairment**: If large or multiple AMLs compromise renal function.
- **Malignant transformation**: Rare, but suspected if tumour grows rapidly or lacks fat content on imaging.

Prognosis

- Generally **excellent** prognosis with appropriate management.
- Regular **imaging follow-up** recommended for large or symptomatic AMLs.
- **mTOR inhibitors** are effective in TSC-associated cases, reducing tumour size and complications.

Bladder cancer

Definition

- Bladder cancer refers to **malignant growths in the urinary bladder**.
- The majority (90%) are **transitional cell carcinomas (urothelial cancers)**.

Epidemiology

- **Fourth most common cancer** in men.
- **Male-to-female ratio**: 3:1.
- Commonly diagnosed in individuals over **65 years**.
- **Higher incidence in smokers** and individuals with occupational exposure.

Risk Factors

- **Smoking** (the most significant risk factor).
- **Occupational exposure** to carcinogens: dyes, rubber, leather, chemicals (e.g., aniline dyes).
- **Chronic bladder inflammation**: schistosomiasis, chronic catheter use.
- **Previous radiation therapy** to the pelvis.
- **Cyclophosphamide** use (chemotherapy).

Pathophysiology

- **Chronic exposure to toxins** in urine causes DNA mutations in bladder epithelium, leading to tumour formation.
- Transitional cell carcinoma arises from **urothelial cells** lining the bladder.

Clinical Features

- **Painless haematuria** (the most common presenting symptom).
- **Dysuria, frequency**, or **urgency** (in advanced or invasive disease).
- **Pelvic pain** or **weight loss** (suggestive of metastatic disease).

Diagnosis

1. **Urinalysis**:
    - Detects haematuria.
    - May show malignant cells on **urine cytology**.
2. **Imaging**:
    - **Ultrasound**: Detects masses or bladder wall thickening.
    - **CT urogram**: For staging and detecting upper tract involvement.
3. **Cystoscopy and Biopsy**:
    - **Gold standard** for diagnosis.
    - Allows direct visualisation and biopsy for histology.

Histological Types

- **Transitional cell carcinoma (TCC)**: 90% of cases.
- **Squamous cell carcinoma**: 5% (often associated with schistosomiasis).
- **Adenocarcinoma**: Rare.

Staging

- **Non-muscle invasive bladder cancer (NMIBC)**: Confined to mucosa/submucosa.
- **Muscle-invasive bladder cancer (MIBC)**: Involves muscle layer or deeper tissues.

Complications

- **Obstruction** of ureters leading to **hydronephrosis**.
- **Bladder perforation**.
- **Metastasis**: Commonly to lymph nodes, bones, liver, and lungs.

Management

Treatment Modality	Indications
Transurethral resection of bladder tumour (TURBT)	For NMIBC (non-muscle invasive). Followed by intravesical chemotherapy.
Intravesical Bacillus Calmette-Guérin (BCG)	Used to prevent recurrence in high-risk NMIBC.
Intravesical chemotherapy (e.g., mitomycin C)	For intermediate-risk NMIBC.
Radical cystectomy	For MIBC or high-risk recurrent NMIBC.
Neoadjuvant chemotherapy	Given before surgery to shrink tumour size (e.g., cisplatin-based).
Radiotherapy	Alternative to surgery for inoperable cases.
Systemic chemotherapy (e.g., gemcitabine + cisplatin)	For metastatic bladder cancer.
Immunotherapy (e.g., pembrolizumab)	Used in advanced or metastatic cases with PD-L1 expression.

Prognosis

- **5-year survival rate**:
  - **Non-muscle invasive**: 90%.
  - **Muscle-invasive**: 50-60%.
  - **Metastatic**: Poor prognosis, <10%.
- **Regular follow-up** with cystoscopy is essential due to the **high recurrence rate** of bladder cancer.

> **Use of cyclophosphamide in granulomatosis with polyangiitis is associated with increased risk of bladder cancer (transitional cell carcinoma)**

Urinary tract infection (UTI)

Classification of UTI (European association of urology guidelines)	
Uncomplicated UTIs	Infection in nonpregnant, premenopausal women without further risk factors for infection, treatment failure, or serious outcomes
Complicated UTIs	All UTIs which are not defined as uncomplicated. UTIs in a patient with risk factors for a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, **indwelling urinary catheters**, renal diseases, and/or with other concomitant immunocompromising diseases (e.g. **diabetes**)
Lower UTI	Infection of the bladder (cystitis), the most common location of UTIs. Often accompanied by urethritis (urethritis in isolation is suggestive of STI). Can be associated with prostatitis in men
Upper UTI	Infection of the kidneys and ureter (pyelonephritis)
Recurrent UTIs	≥ 3 episodes of symptomatic, culture-proven UTI in one year or ≥ 2 episodes in 6 months
Catheter-associated UTIs	UTIs in a person **currently** catheterised or has been catheterised **within the past 48 hours**.
Urosepsis	UTI accompanied by signs of systemic inflammation, features of organ dysfunction and persistent hypotension associated with tissue anoxia.

Comparison of UTI in Males vs Females

Feature	Females	Males
Incidence	Much higher, especially in younger and sexually active women	Less common, increases with age (especially >50 years)
Anatomical factors	Shorter urethra increases the risk of infection	Longer urethra provides protection against infections
Risk factors	Sexual activity, pregnancy, menopause	Prostatic enlargement, urinary obstruction, catheter use
Pathogens	**Escherichia coli** (most common), **Staphylococcus saprophyticus**	**Escherichia coli, Proteus mirabilis, Enterococcus**
Symptoms	Dysuria, frequency, urgency, suprapubic pain	Dysuria, frequency, urgency, suprapubic pain, perineal discomfort
Complications	Pyelonephritis, recurrent UTI, pregnancy complications	Prostatitis, epididymitis, sepsis, recurrent UTI
Diagnosis	Urinalysis, urine culture (clean-catch sample)	Urinalysis, urine culture, consider prostate examination
Management	Nitrofurantoin, Trimethoprim, Cefalexin	Ciprofloxacin, Trimethoprim, Amoxicillin (adjusted based on prostate involvement)
Treatment duration	3-5 days (uncomplicated), 7-10 days (complicated)	7-14 days (often longer due to potential prostate involvement)
Prognosis	Generally good with appropriate treatment	Longer treatment needed, higher risk of complications in older males

Comparison Between Lower and Upper Urinary Tract Infections (UTI)

Feature	Lower UTI (Cystitis, Urethritis)	Upper UTI (Pyelonephritis)
Definition	Infection of the bladder and/or urethra	Infection of the kidneys (renal pelvis and parenchyma)
Location	Bladder and urethra	Kidneys and upper urinary tract
Common Symptoms	- Dysuria (painful urination) - Urinary frequency and urgency - Suprapubic pain - Hematuria	- Fever and chills - Flank or costovertebral angle pain - Nausea and vomiting - Dysuria and urinary frequency (may coexist)
Systemic Symptoms	Generally absent	Common (fever, chills, malaise)
Complications	Rare	Sepsis, renal abscess, kidney damage
Urine Dipstick Findings	- Positive leukocyte esterase - Positive nitrites	- Same as lower UTI - May show casts in urine
Urine Culture	Positive with bacterial growth (>10^5 CFU/mL)	Positive with bacterial growth (>10^5 CFU/mL)
Diagnostic Imaging	Not usually required	Recommended if complicated (e.g., ultrasound, CT scan)
First-Line Treatment	Nitrofurantoin 100 mg BD for 5 days TMP-SMX 160/800 mg BD for 3 days	Ciprofloxacin 500 mg BD for 7 days Levofloxacin 750 mg daily for 5 days
Duration of Treatment	3–7 days (depends on severity and patient factors)	7–14 days (longer for complicated cases)
Complicated UTI	Less likely	More likely to develop in high-risk patients (e.g., elderly, diabetics)
Common Causes	Escherichia coli, Staphylococcus saprophyticus	Escherichia coli, Klebsiella, Proteus species
Risk of Recurrence	High, especially in females	Less common but may occur in patients with anatomical abnormalities or untreated infection
Need for Hospitalisation	Rarely required	May require hospitalisation if severe or if associated with sepsis

Causes

- **Escherichia coli:** the most common cause (80%)
- **Staphylococcus saprophyticus:** 2nd common cause in sexually active women
- **Klebsiella pneumoniae:** 3rd common cause
- **Proteus mirabilis:** Produces ammonia, giving the urine a pungent or irritating smell
  Associated with struvite stone formation
- **P - Pseudomonas**

Predisposing factors

- **Structural or functional abnormalities of the urinary tract** →urinary stasis (e.g, BPH, congenital malformations causing vesicoureteral reflux, bladder diverticulum, neurogenic bladder, calculi)
- **Female** (short urethra → bacteria spread from the anus)
- **Pregnancy:** hormonal changes during pregnancy → urinary stasis and vesicoureteral reflux.
- **Postmenopause:** ↓ estrogen → ↓ vaginal lactobacilli → ↑ vaginal pH → ↑ colonization by E. coli
- **Immunosuppression, DM**
- **Sexual intercourse:** postcoital cystitis (honeymoon cystitis)
- **Catheter-associated urinary tract infection (CAUTI):** Most common cause of nosocomial UTI.

Investigations

Investigation	Findings	Purpose
Urine Dipstick Test	- Positive leukocyte esterase (WBC presence) - Positive nitrites (indicates Gram-negative bacteria like *E. coli*) - Hematuria (blood)	Quick screening test to suggest UTI.
Urinalysis (Microscopy)	- Pyuria: >5 WBCs/high-power field - Bacteriuria: Bacteria present in uncentrifuged urine	Detects infection and inflammation.
Urine Culture and Sensitivity	- Significant bacteriuria: $>10^5$ CFU/mL in clean-catch sample (asymptomatic) - Lower thresholds accepted for symptomatic patients	Confirms the causative pathogen and provides antibiotic sensitivity.
Blood Tests (CBC)	- Leukocytosis (high WBC count)	May indicate systemic infection or pyelonephritis.
Blood Culture	- Positive for bacteremia (urosepsis)	Useful in severe or upper UTI.
Ultrasound (US)	- Detects structural abnormalities, abscesses, or stones	Useful in complicated or recurrent UTI cases.
CT Scan (with contrast)	- Identifies obstruction, abscess, or severe pyelonephritis	Used for complicated UTI or poor response to treatment.
Urine Sample from Catheter	- Positive culture from sample taken directly from catheter	Essential for diagnosing catheter-associated UTI.
Pregnancy-Specific Screening	- Urine culture: Asymptomatic bacteriuria $>10^5$ CFU/mL	Screening is mandatory during pregnancy.

Management

Antibiotic Guidelines for Urinary Tract Infection (UTI) Based on Latest UK Guidelines

Scenario	First-Line Treatment	Alternative Treatment
Uncomplicated UTI (non-pregnant women)	Nitrofurantoin 100 mg modified-release BD for 3 days (if eGFR ≥45 mL/min)	Trimethoprim 200 mg BD for 3 days (if low resistance risk)
Uncomplicated UTI (men)	Nitrofurantoin 100 mg modified-release BD for 7 days (if eGFR ≥45 mL/min)	Trimethoprim 200 mg BD for 7 days Pivmecillinam 400 mg initially, then 200 mg TDS for 7 days
Recurrent UTI (≥2 infections in 6 months)	Nitrofurantoin 50–100 mg once daily for 3–6 months (prophylaxis)	Trimethoprim 100 mg once daily for 3–6 months (prophylaxis)
Pregnant women (asymptomatic bacteriuria or UTI)	Nitrofurantoin 100 mg modified-release BD for 7 days (avoid after 36 weeks)	Cefalexin 500 mg BD or TDS for 7 days
Complicated UTI	Nitrofurantoin 100 mg modified-release BD for 7 days (if eGFR ≥45 mL/min)	Co-amoxiclav 500/125 mg TDS for 7 days Ciprofloxacin 500 mg BD for 7 days
Pyelonephritis (acute upper UTI)	Cefalexin 500 mg TDS for 7–10 days	Ciprofloxacin 500 mg BD for 7 days Co-amoxiclav 500/125 mg TDS for 7–10 days
Catheter-associated UTI (symptomatic)	Nitrofurantoin 100 mg modified-release BD for 7 days (if catheter removed)	Cefalexin 500 mg TDS for 7 days Co-amoxiclav 500/125 mg TDS for 7 days

Important Considerations

- **Nitrofurantoin**: Avoid if eGFR <45 mL/min due to low renal clearance.
- **Pregnancy**: Avoid **nitrofurantoin** after 36 weeks to prevent neonatal haemolysis.
- **Trimethoprim**: Avoid in the first trimester unless folate deficiency is excluded.
- **Ciprofloxacin**: Use with caution due to risk of tendon rupture; reserve for severe infections.
- **Prophylaxis**: Consider long-term low-dose antibiotics in recurrent UTIs.
- **Catheter-related UTI**: Remove or replace catheter when possible to enhance treatment outcomes.

Extended Spectrum Beta-Lactamase (ESBL) UTI

Definition and Mechanism:

- ESBL-producing bacteria are resistant to most beta-lactam antibiotics, including penicillins and cephalosporins, due to the production of enzymes that hydrolyse these antibiotics. *Escherichia coli* and *Klebsiella pneumoniae* are the most common causes. These bacteria often have additional resistance to other antibiotic classes like fluoroquinolones and aminoglycosides, complicating treatment.

Risk Factors:

- Hospitalisation or long-term care facility stay
- Recent antibiotic use, especially beta-lactams and fluoroquinolones
- Urinary catheters or urological interventions
- History of recurrent UTIs
- Immunosuppression or chronic illness (e.g., diabetes)

Diagnosis: Urine culture and sensitivity testing:
Management:
First-line Treatment Options:

- **Carbapenems** (e.g., Meropenem 1 g IV every 8 hours for severe cases)
    - Effective against most ESBL-producing organisms.
- **Fosfomycin** (3 g orally, single dose for uncomplicated cystitis)
    - Suitable for lower UTI.
- **Nitrofurantoin** (100 mg orally BD for 5–7 days)
    - For uncomplicated cystitis, not effective in pyelonephritis.

Alternative Treatments:

- **Piperacillin-tazobactam**: For less severe infections if susceptibility confirmed.
- **Aminoglycosides** (e.g., Gentamicin) can be used as adjunct therapy in severe infections.

Renal Tuberculosis

Aspect	Details
Definition	Renal tuberculosis is an extrapulmonary TB caused by hematogenous spread of **Mycobacterium tuberculosis** to the kidneys.
Epidemiology	- Common in endemic TB areas. - Affects adults more than children. - A frequent site of extrapulmonary TB.
Pathophysiology	- **Hematogenous spread** from a primary pulmonary focus. - Granuloma formation → caseation, cavitation, and fibrosis in renal tissue.
Clinical Features	- **Early (non-specific)**: Malaise, fever, weight loss, night sweats. - **Renal symptoms**: Dysuria, frequency, flank pain, sterile pyuria.
Complications	- Hydronephrosis, stricture formation. - Chronic kidney disease (CKD). - Genital TB: Epididymitis, infertility.
Diagnosis	- **Urine Microscopy**: Sterile pyuria, AFB on Ziehl-Neelsen stain. - **Urine Culture**: Mycobacterial culture (gold standard). - **PCR for TB**: Rapid, sensitive. - **Imaging**: Ultrasound, IVU/CT Urogram for cavitations, strictures, or calcifications. - **Other Tests**: Tuberculin skin test (TST), IGRA, chest X-ray for pulmonary TB.
Management	- **Anti-TB Therapy (ATT)**: - Isoniazid, Rifampicin, Pyrazinamide, Ethambutol (6–9 months). - **Surgery**: For complications (strictures, non-functioning kidney); nephrectomy for severe damage.
Prognosis	- **Good**: Early diagnosis and ATT. - **Poor**: Delayed treatment, extensive renal damage, or progression to CKD.

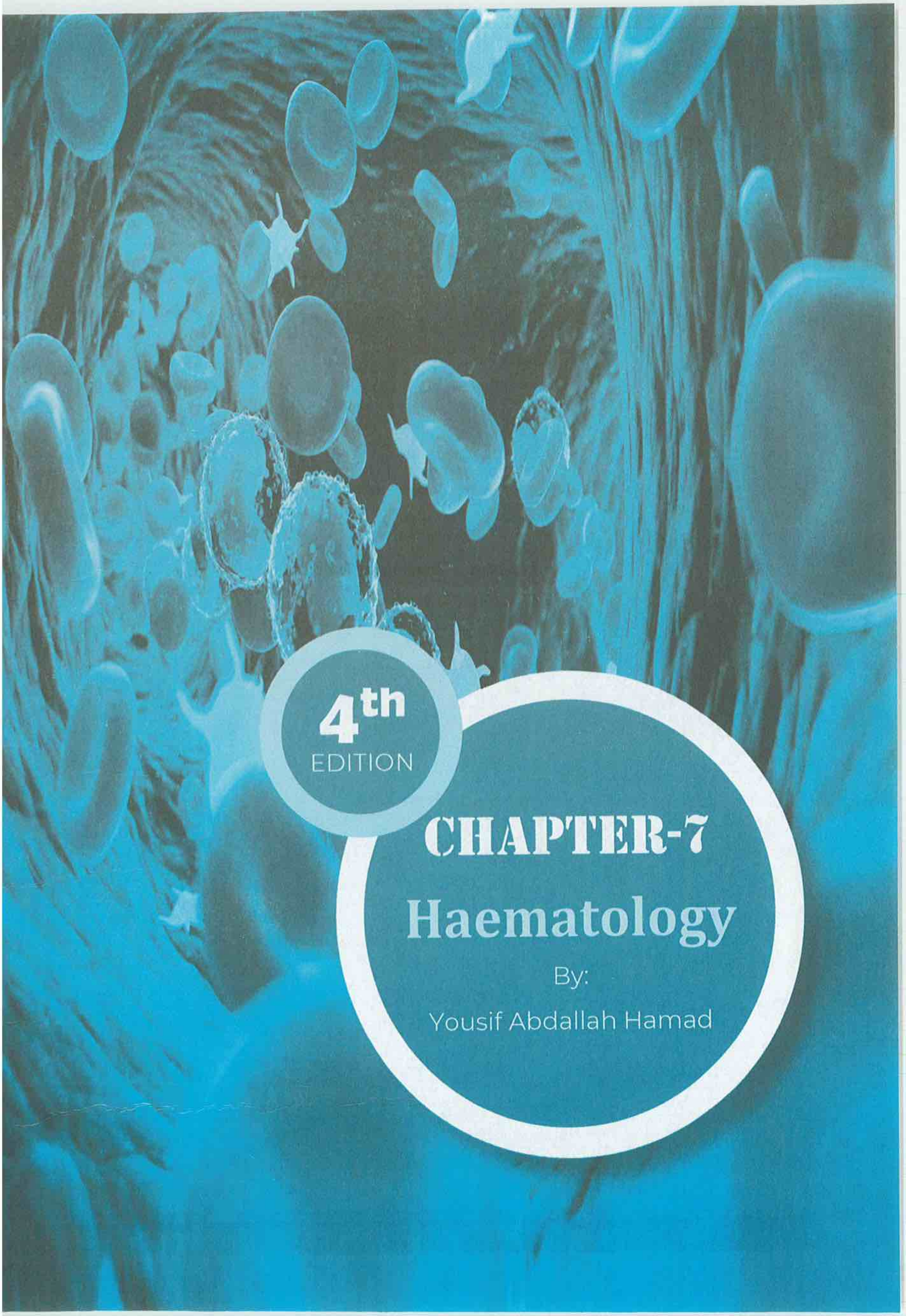
Vesico-Ureteric Reflux (VUR)

Aspect	Details
Definition	Abnormal retrograde flow of urine from the bladder into the ureters and possibly the kidneys.
Classification	- **Primary VUR**: Congenital defect in vesico-ureteric junction (VUJ). - **Secondary VUR**: Due to bladder dysfunction (e.g., obstruction, neurogenic bladder, or infections).
Epidemiology	- Common in children. - More frequent in boys during infancy but more common in girls after infancy. - Associated with UTIs.
Pathophysiology	- Failure of the **VUJ valve mechanism**, allowing urine to reflux. - Leads to renal scarring, recurrent UTIs, and hydronephrosis.
Grading (International Reflux Study)	- **Grade I**: Reflux into ureter only. - **Grade II**: Reflux into ureter and renal pelvis without dilation. - **Grade III**: Mild to moderate ureteral and renal pelvis dilation. - **Grade IV**: Moderate dilation with blunting of calyces. - **Grade V**: Severe dilation and tortuosity of ureter with loss of calyceal definition.
Clinical Features	- Recurrent **UTIs** (most common presentation). - Fever, dysuria, and abdominal/flank pain. - Failure to thrive in severe cases. - **Complications**: Renal scarring, hypertension, and chronic kidney disease (CKD).
Diagnosis	- **Voiding Cystourethrogram (VCUG)**: Gold standard. - **Renal Ultrasound**: Detects hydronephrosis or scarring. - **DMSA Scan**: Detects renal scarring and functional impairment. - **Urine Culture**: Confirms UTI.
Management	- **Medical**: - Low-dose prophylactic antibiotics for recurrent UTIs. - Regular monitoring with imaging and urine cultures. - **Surgical**: - Ureteral reimplantation (for severe or persistent VUR). - Endoscopic injection of bulking agents (e.g., Deflux) at VUJ.
Prognosis	- Many cases of low-grade VUR resolve spontaneously with growth. - High-grade VUR has a higher risk of complications, requiring surgical intervention.

Urethral Syndrome

Aspect	Details
Definition	A condition characterized by **lower urinary tract symptoms (LUTS)**, such as dysuria, frequency, and urgency, without evidence of urinary tract infection (UTI) on standard culture.
Epidemiology	- More common in women than men. - Often affects sexually active individuals or postmenopausal women.
Aetiology	- **Infectious Causes**: - Atypical pathogens (e.g., Chlamydia, Ureaplasma, Mycoplasma). - **Non-Infectious Causes**: - Local irritation (e.g., spermicides, hygiene products). - Hormonal changes (e.g., menopause, atrophic vaginitis). - Urethral trauma (e.g., catheterization, sexual activity). - Interstitial cystitis or pelvic floor dysfunction.
Pathophysiology	- Inflammation or irritation of the urethra without a detectable infection on conventional urine culture. - May involve mucosal hypersensitivity or epithelial damage.
Clinical Features	- **LUTS**: - Dysuria, frequency, urgency. - Suprapubic discomfort. - Perineal pain or burning. - **Key Feature**: No significant bacteriuria ($<10^5$ CFU/mL).
Diagnosis	- **Exclusion of UTI**: - Negative urine culture. - Atypical pathogens (consider nucleic acid amplification tests for STIs). - **Urinalysis**: Sterile pyuria may be present. - **Pelvic Examination**: Rule out atrophic vaginitis or genital infections. - **Cystoscopy**: Consider for recurrent or persistent symptoms to exclude interstitial cystitis or urethral abnormalities.
Management	- **Lifestyle Modifications**: - Avoid irritants (e.g., soaps, douches). - Increase fluid intake. - **Medications**: - Empirical antibiotics (for suspected atypical infections, e.g., doxycycline, azithromycin). - Topical oestrogen (postmenopausal women). - Nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief. - **Pelvic Floor Therapy**: - Physiotherapy for pelvic floor dysfunction. - **Refractory Cases**: - Consider referral to a urologist for further evaluation.
Prognosis	- Most cases resolve with appropriate management. - Persistent symptoms may require further investigation for interstitial cystitis or pelvic pain syndromes.

This page is intentionally left blank



4th EDITION

CHAPTER-7

Haematology

By:

Yousif Abdallah Hamad

Iron Metabolism

Iron Distribution in the Body:

- **Total Body Iron**: ~3–5 g in adults.
  - **Haemoglobin (Hb)**: ~65–70%.
  - **Storage Iron**: ~25–30% (as ferritin and haemosiderin in liver, spleen, and bone marrow).
  - **Myoglobin**: ~5%.
  - **Enzymes**: ~1–2% (e.g., cytochromes, catalase).
  - **Plasma Iron (Bound to Transferrin)**: ~0.1%.

Sources of Iron:

- **Dietary Iron**:
  - Heme Iron (animal sources): Absorbed efficiently.
  - Non-Heme Iron (plant sources): Less efficiently absorbed.
- **Daily Requirement**:
  - **Men**: 8–10 mg/day.
  - **Women (premenopausal)**: 15–20 mg/day.
  - **Pregnancy**: ~30 mg/day.

Iron Absorption:

- **Site**: Duodenum and proximal jejunum.
- **Process**:
  1. **Heme Iron**: Absorbed intact via specific receptors.
  2. **Non-Heme Iron**:
     - Reduced to **ferrous iron (Fe^{2+})** by **duodenal cytochrome b**.
     - Transported into enterocytes via **DMT-1 (divalent metal transporter-1)**.
- Inside Enterocytes:
  - Stored as ferritin or transported into circulation by **ferroportin** (iron exporter).
- **Regulation**:
  - **Hepcidin**: A liver-derived peptide that inhibits ferroportin, reducing iron absorption and release from stores.

Transport of Iron:

- **Transferrin**:
  - Binds ferric iron (Fe^{3+}) for transport in plasma.
  - Transferrin saturation: Normally ~30%.
- Iron is delivered to tissues via **transferrin receptors (TfR)**.

Storage of Iron:

- **Ferritin**:
  - Soluble iron-storage protein in liver, spleen, and bone marrow.
  - Reflects iron stores (serum ferritin correlates with body iron).
- **Haemosiderin**:
  - Insoluble form of storage iron, especially in iron overload.

Utilisation of Iron:

- **Haemoglobin Synthesis**:
    - Iron is essential for oxygen transport.
- **Enzymatic Reactions**:
    - Cytochromes (oxidative phosphorylation).
    - Catalase and peroxidase (free radical defence).

Loss of Iron:

- **Physiological Loss**:
    - ~1–2 mg/day (via shedding of enterocytes, skin cells, and menstruation).
- No active excretory pathway; iron balance depends on regulation of absorption.

Regulation of Iron Homeostasis:

- **Hepcidin**:
    - Inhibits ferroportin, reducing intestinal iron absorption and mobilization from macrophages.
    - Increased by inflammation (causing anaemia of chronic disease).
    - Decreased by hypoxia, iron deficiency, or increased erythropoietic activity.

Disorders of Iron Metabolism:

Condition	Pathophysiology	Findings
Iron Deficiency Anaemia	Inadequate iron intake, absorption, or chronic blood loss.	Low Hb, ferritin, transferrin saturation; high TIBC.
Anaemia of Chronic Disease	Hepcidin-mediated iron sequestration.	Low serum iron, transferrin; normal/high ferritin; low TIBC.
Hereditary Haemochromatosis	Excess iron absorption due to HFE mutation.	High serum iron, ferritin, transferrin saturation; iron deposition in organs (liver, heart, joints).
Sideroblastic Anaemia	Defective incorporation of iron into haem.	Ringed sideroblasts in bone marrow; high ferritin and transferrin saturation.

Key Laboratory Parameters:

Test	Normal Range	Significance
Serum Iron	10–30 µmol/L (55–160 µg/dL)	Low in deficiency, inflammation.
TIBC (Total Iron Binding Capacity)	45–70 µmol/L (250–400 µg/dL)	High in deficiency; low in chronic disease.
Transferrin Saturation	20–50%	Low in deficiency; high in haemochromatosis.
Ferritin	15–300 µg/L	Low in deficiency; high in chronic disease or overload.

Key Points for MRCP:

1. **Iron absorption** is regulated by hepcidin and is the primary site of iron homeostasis control.
2. Iron deficiency is the most common nutritional deficiency worldwide, often secondary to blood loss.
3. **Transferrin saturation** and **ferritin** are essential tests for differentiating iron deficiency from other anaemias.
4. Chronic inflammation increases hepcidin, contributing to anaemia of chronic disease.

Oral iron absorption.

A. Effectors of iron absorption.	
Inhibiting iron absorption	**Facilitating iron absorption**
• **Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages** • **Multivitamin or dietary supplements containing calcium, zinc, manganese or copper** • **Antacids, H2 blockers and proton pump inhibitors.** • **Quinolones and tetracycline antibiotics**	• **Vitamin C** • **Acidic foods e.g. tomato sauce** • **Non enteric coated iron tablets** • **Fasting ingestion of iron supplements**
B. Oral iron absorption test.	
Step 1: Measure morning serum iron level (fasting).	
Step 2: Ingest approximately 60mg elemental iron (324 mg ferrous sulphate) with water.	
Step 3: After 1-2 hours, measure the serum iron level.	
Step 4: Compare the serum iron levels.	
Interpretation: An increase in serum iron of >100 µg/dL suggests gut absorption is generally adequate.	

Iron Absorption, Transport, and Regulation

Dietary Iron:

The body requires 10–20 mg of daily iron intake, present in two forms: ferrous (Fe^{2+}) and ferric (Fe^{3+}).

Dietary sources should include both **haem iron** (animal-based, higher bioavailability) and **non-haem iron** (plant-based, enhanced by vitamin C intake).

Absorption:

Iron is absorbed in the small intestine, primarily in its ferric form, but must be converted to ferrous iron by **Vitamin C ferro reductase** for proper uptake via **DMT1 channels** into enterocytes.

Transport:

After absorption, ferrous iron is converted back to ferric iron for transport in the bloodstream by transferrin, a key protein ensuring proper iron distribution and homeostasis.

Erythropoiesis:

About 75% of absorbed iron is used for red blood cell production in the bone marrow, underscoring its role in oxygen transport via haemoglobin.

Storage:
Excess iron is stored in the liver as ferritin. Transferrin binds to receptors to deliver iron for storage or utilisation.
Regulation:
Hepcidin, a hormone produced by the liver, regulates iron balance by inhibiting **ferroportin**, a transporter responsible for iron export from cells, controlling plasma iron levels.
Recycling:
Macrophages in the spleen recycle iron from old or damaged red blood cells, contributing to erythropoiesis.
Inflammation and Genetics: Hepcidin levels are influenced by inflammatory cytokines (e.g., interleukin-6) and genetic mutations in the **HFE gene**. Mutations can lead to hereditary haemochromatosis and iron overload.

NORMAL IRON STORES

The normal iron content of the body is 3 to 4 grams, distributed as follows:
- Hemoglobin in RBCs – 2.5 grams
- Iron-containing proteins other than hemoglobin (eg, myoglobin, cytochromes, catalase) – 400 mg
- Iron bound to circulating transferrin – 3 to 7 mg
- **Storage**
  - ⇨ Storage iron in the form of ferritin or hemosiderin (typically in bone marrow macrophages)
  - ⇨ Adult males have approximately 1 g of storage iron (mostly in liver, spleen, and bone marrow). Adult females often have less storage iron, depending upon the menses, pregnancies, deliveries, and iron intake; some may have no iron stores.
  - ⇨ **causes of increased iron stores** include hereditary hemochromatosis , ineffective erythropoiesis (eg, in thalassemia), and a large number of red blood cell transfusions

Total body iron content is determined by the balance between dietary iron intake (or other sources such as transfusion) and iron loss from bleeding or shedding of iron-containing cells; **there are no physiologic mechanisms to eliminate iron from the body when it is present in excess:**
- **Intake** – A typical diet contains approximately 10 to 20 mg of iron;
  - ⇨ 10% absorbed in the upper GIT.
  - ⇨ Heme iron (eg, iron in meats) is better absorbed than non-heme iron (eg, iron from vegetable sources).
- **Absorption**
  - ⇨ absorption of iron from intestinal cells and the release of storage iron from macrophages is highly controlled, in a process involving a number of transport proteins and their regulators.
  - ⇨ hereditary hemochromatosis (C282Y variant mutation in the *HFE* gene) leads to excessive intestinal iron absorption
- **Loss** –
  - ⇨ Iron is normally lost in sweat, shed skin cells, and gastrointestinal loss at a rate of approximately 1 mg/day.
  - ⇨ Menstruating females lose additional iron, equivalent to 0.5 to 1.0 mg/day.
  - ⇨ removal of iron from the body is not regulated.
- **Recycling** – Iron is recycled from the breakdown of senescent RBCs in the macrophages of the reticuloendothelial system in the liver, spleen, and bone marrow.

Approach to the patient with suspected iron overload

Importance:

- Iron overload is a **serious** problem, often **overlooked** because of **nonspecific** symptoms and **gradual development.**
- untreated Iron overload leads to life-threatening organ toxicity. It is important to identify iron overload before organ damage occurs.

Causes of Iron Overload and Mechanisms

Cause	Mechanism
Increased Intake	
- Repeated Blood transfusion	Iatrogenic; to treat severe anaemia (thalassemia, sickle cell disease)
- **Iron-loaded diet** ("African iron overload")	Dietary
- **Repeated hemin infusions** (e.g., for acute intermittent porphyria)	Iatrogenic; treat acute porphyric attacks.
Increased Absorption (with Normal Intake)	
- **Hereditary haemochromatosis** (HFE C282Y homozygosity)	Reduced hepcidin, leading to excessive iron absorption.
- **Thalassaemia major or intermedia**	Ineffective erythropoiesis suppresses hepcidin; transfusional iron overload may also occur.
- **Sideroblastic anaemia** (inherited or acquired)	Ineffective erythropoiesis suppresses hepcidin, increasing iron absorption.
- **Chronic liver disease** (e.g., alcohol-associated fatty liver, chronic hepatitis, metabolic dysfunction-associated steatotic liver disease)	Mechanism incompletely understood; possible reduced hepcidin.

Complications

- Hepatic involvement with biochemical abnormalities in liver function, inflammation, fibrosis, and eventually cirrhosis
- Cardiac involvement with cardiomyopathy, heart failure, and/or arrhythmias
- Pancreatic involvement with diabetes mellitus
- Pituitary and gonadal involvement with hypogonadism, decreased libido, and impotence
- Skin involvement with hyperpigmentation ("bronze diabetes")
- Joint involvement with arthropathy, especially involving the second and third metacarpophalangeal joints, and often with chondrocalcinosis

Diagnosis

Indication for iron overload evaluation: Suspect iron overload in the following:

- Family history of hereditary hemochromatosis (HH)
- Multiple RBC transfusions for blood loss or anemia other than iron deficiency
- Unexplained organ damage such as liver, heart, endocrine, or joint disease
- Incidental finding of increased serum ferritin or transferrin saturation (TSAT)

Testing approach

Sequence and Interpretation of Testing for Iron Overload

1. Initial Laboratory Evaluation

All patients with suspected iron overload should undergo:

- **Complete Blood Count (CBC):** Includes red blood cell (RBC) indices and reticulocyte count.
- **Iron Studies:** Serum ferritin and transferrin saturation (TSAT).
- **Metabolic Panel:** Hepatic enzymes (ALT, AST).

2. Interpretation of CBC and Iron Studies

- **Normal CBC with Elevated Ferritin and TSAT:**
  - Suggests hereditary haemochromatosis (HH) or other iron overload conditions.
- **Microcytic Anaemia with Elevated Ferritin and TSAT:**
  - Indicates thalassaemia (transfusion-dependent or non-transfusion-dependent).
- **Normocytic Anaemia with Elevated Reticulocyte Count:**
  - Suggests haemolytic anaemia.
- **Normocytic Anaemia with Elevated Ferritin:**
  - Suggests anaemia of chronic disease or inflammation.
- **Macrocytic Anaemia with Elevated Ferritin and/or TSAT:**
  - Associated with causes such as vitamin B12 deficiency or haemolysis.
- **Polycythaemia with Elevated Ferritin and/or TSAT:**
  - Suggests erythrocytosis due to hypoxia, erythropoietin overproduction, or polycythaemia vera.

3. Additional Testing

- **HFE Genetic Testing:**
  - Indicated for individuals with laboratory evidence of iron overload, especially with a family history of HH.
  - Detects common mutations (e.g., C282Y and H63D) to identify hereditary causes.
- **Liver Function Tests (LFTs):**
  - Helpful in distinguishing iron overload related to liver disease.
- **Non-invasive Imaging (MRI):**
  - **Liver MRI:** Detects hepatic iron concentration (>3 mg Fe/g dry liver weight indicates overload).
  - **Cardiac MRI:** Assesses myocardial iron deposition (T2* <20 ms indicates cardiac iron overload).
- **Liver Biopsy:**
  - Rarely required but useful for histological assessment and quantification of hepatic iron content.

4. Diagnostic Criteria

- **Iron Studies:**
  - Elevated serum ferritin (≥200–300 ng/mL in males, ≥150–200 ng/mL in females).
  - TSAT ≥45% (males) or ≥40% (females).
- **MRI:**
  - Liver iron >2 mg Fe/g dry weight or cardiac T2* <20 ms.
- **Liver Biopsy:**
  - Iron deposition (>2 mg Fe/g dry weight).

- **Phlebotomy Response:**
  - Normalisation of ferritin after therapeutic phlebotomy supports iron overload diagnosis.

5. Differential Diagnosis

- **Elevated Ferritin Without Iron Overload:**
  - Acute illnesses (e.g., haemophagocytic lymphohistiocytosis, HIV).
  - Chronic inflammatory conditions (e.g., metabolic syndrome, diabetes).
  - Liver diseases (e.g., hepatitis, alcoholic liver disease).
  - Malignancies (e.g., haematologic cancers).
  - Genetic conditions (e.g., hereditary hyperferritinaemia-cataract syndrome).
- **Other Organ Dysfunction Causes:**
  - Heart disease, diabetes, or hypogonadism unrelated to iron overload.

6. Post-Diagnostic Testing

- **Extent of Iron Overload:**
  - Serum ferritin, MRI (liver and cardiac), and response to phlebotomy assess total iron burden.
  - Significant risk of complications with total body iron stores >5 grams or liver iron >7 mg/g dry weight.
- **Underlying Cause:**
  - Review family history, genetic testing (HFE), and comorbid conditions (e.g., liver disease, transfusion history).

7. Management-Related Considerations

- **Therapeutic Phlebotomy:**
  - Used to estimate total body iron stores when non-invasive methods are unavailable.
- **HFE Testing for Relatives:**
  - Genetic screening recommended for first-degree relatives of individuals with HH.

Key Points

- Comprehensive evaluation includes CBC, iron studies, LFTs, genetic testing, and imaging.
- Distinguishing between hereditary and acquired causes of iron overload is crucial for treatment planning.
- MRI is the preferred non-invasive method for quantifying iron burden in the liver and heart.

Haematological changes during pregnancy

Haemoglobin (Hb) and Red Blood Cells (RBCs):

- **Plasma Volume Expansion**:
  - Increases by 40–50% by the third trimester.
- **Red Cell Mass Expansion**:
  - Increases by 20–30%, stimulated by erythropoietin production.
- **Haemodilution** (Physiological Anaemia of Pregnancy):
  - Hb levels decrease due to disproportionate plasma volume expansion compared to RBC mass.
  - **Normal Hb Values**:
    - **1st trimester**: ≥110 g/L.
    - **2nd trimester**: ≥105 g/L.
    - **3rd trimester**: ≥110 g/L.
  - **MCV**: Often normal or slightly increased.

White Blood Cells (WBCs):

- **Leukocytosis**:
  - WBC count increases progressively during pregnancy.
  - **Range**: 6–16 × 10^9/L.
  - Neutrophilia is predominant; lymphocyte count may decrease slightly.
  - **Clinical Importance**: A mild increase in WBC count is physiological, but marked leukocytosis may indicate infection.

Platelets (Thrombocytes):

- **Mild Thrombocytopenia** (Gestational Thrombocytopenia):
  - Platelet count decreases due to haemodilution and increased platelet turnover.
  - **Normal Count**: ≥150 × 10^9/L.
  - Platelet counts typically remain >100 × 10^9/L.
  - **Clinical Importance**: Persistent thrombocytopenia <100 × 10^9/L warrants evaluation for pathological causes (e.g., preeclampsia, HELLP syndrome, or immune thrombocytopenia).

Coagulation and Fibrinolysis:

- **Hypercoagulable State**:
  - Increased levels of pro-coagulant factors (factors VII, VIII, IX, X, XII, and fibrinogen).
  - Decreased levels of natural anticoagulants (e.g., protein S).
  - Reduced fibrinolytic activity.
  - **Fibrinogen**: Increases to 4–6 g/L (normal non-pregnant range: 2–4 g/L).
  - **Clinical Importance**: Increased risk of venous thromboembolism (VTE) during pregnancy and puerperium.

Iron and Folate Metabolism:

- **Iron**:
  - Increased demand (~1,000 mg total during pregnancy).
  - Iron deficiency anaemia (IDA) is common if supplementation is not provided.
  - **Serum Ferritin**: Decreases as pregnancy progresses.

- **Folate**:
  - Increased demand for DNA synthesis.
  - Deficiency can lead to megaloblastic anaemia.

Erythrocyte Sedimentation Rate (ESR):

- Elevated in pregnancy due to increased plasma proteins (e.g., fibrinogen).
- **Normal ESR in Pregnancy**:
  - **1st half**: Up to 40 mm/hr.
  - **2nd half**: Up to 70 mm/hr.

Pathological Red Cell Forms and Diagnostic Associations

Red Cell Form	Description	Associated Conditions
Spherocytes	Round, lack central pallor; smaller than normal red cells.	**Hereditary spherocytosis**, **Autoimmune hemolytic anemia**
Schistocytes	Fragmented cells with irregular shapes (e.g., helmet cells, triangle shapes).	**Microangiopathic hemolytic anemia (MAHA)**: DIC, TTP, HUS; **Mechanical hemolysis** (prosthetic heart valves)
Target Cells	Central bullseye appearance due to excess membrane relative to cell volume.	**Liver disease**, **Thalassemia**, **Hemoglobinopathies** (e.g., HbC disease), **Iron deficiency**
Elliptocytes	Elongated, oval-shaped cells.	**Hereditary elliptocytosis**, **Iron deficiency anemia**, **Megaloblastic anemia**
Stomatocytes	Red cells with a slit-like central pallor.	**Liver disease**, **Alcoholism**, **Hereditary stomatocytosis**
Acanthocytes	Spiky, irregular projections from the red cell surface.	**Liver disease** (e.g., cirrhosis), **Abetalipoproteinemia**, **Neuroacanthocytosis syndromes**
Burr Cells (Echinocytes)	Red cells with short, uniform projections around the cell membrane.	**Uremia**, **Chronic kidney disease**, **Pyruvate kinase deficiency**, **Artifact (in vitro)**
Tear Drop Cells (Dacrocytes)	Teardrop or pear-shaped cells.	**Myelofibrosis**, **Thalassemia**, **Bone marrow infiltration (e.g., malignancy, granulomatous diseases)**
Sickle Cells	Crescent-shaped cells with pointed ends.	**Sickle cell disease**
Howell-Jolly Bodies	Small nuclear remnants inside red cells.	**Post-splenectomy**, **Severe hemolytic anemia**, **Megaloblastic anemia**
Heinz Bodies	Denatured hemoglobin precipitates within red cells, seen with special staining.	**G6PD deficiency**, **Unstable hemoglobinopathies**
Basophilic Stippling	Blue granules within red cells, representing ribosomal remnants.	**Lead poisoning**, **Thalassemia**, **Sideroblastic anemia**, **Heavy metal toxicity**
Pappenheimer Bodies	Iron granules visible in red cells on special stain (Prussian blue).	**Sideroblastic anemia**, **Post-splenectomy**, **Hemolytic anemia**

Blood Film Findings and Corresponding Diagnoses

The interpretation of peripheral blood films is a vital diagnostic tool in haematology. Below is a summary of key findings, their descriptions, and associated diagnoses:

Finding	Description	Associated Diagnoses
Spherocytes	Small, dense, spherical RBCs lacking central pallor.	**Hereditary Spherocytosis, Autoimmune Haemolytic Anaemia.**
Target Cells	RBCs with a central "bullseye" appearance.	**Liver Disease, Thalassaemia, Iron Deficiency Anaemia, Post-Splenectomy.**
Schistocytes	Fragmented RBCs with irregular shapes.	**Microangiopathic Haemolytic Anaemia (MAHA) (e.g., TTP, HUS, DIC), Prosthetic Valves.**
Burr Cells (Echinocytes)	RBCs with evenly spaced projections.	**Chronic Kidney Disease, Liver Disease, Artifact.**
Acanthocytes	Irregularly spiked RBCs.	**Liver Disease, Abetalipoproteinaemia, Post-Splenectomy.**
Howell-Jolly Bodies	Small, dense nuclear remnants within RBCs.	**Post-Splenectomy, Severe Anaemia, Megaloblastic Anaemia.**
Heinz Bodies	Denatured haemoglobin within RBCs (requires supravital stain).	**G6PD Deficiency, Unstable Haemoglobinopathies.**
Basophilic Stippling	Multiple fine or coarse basophilic granules in RBCs.	**Lead Poisoning, Thalassaemia, Alcoholism, Megaloblastic Anaemia.**
Rouleaux Formation	RBCs stacked like coins.	**Multiple Myeloma, Waldenström Macroglobulinaemia, Chronic Inflammation.**
Teardrop Cells (Dacrocytes)	Teardrop-shaped RBCs.	**Myelofibrosis, Thalassaemia, Megaloblastic Anaemia.**
Elliptocytes	Oval or elliptical RBCs.	**Hereditary Elliptocytosis, Iron Deficiency Anaemia.**
Macrocytes	Enlarged RBCs (MCV >100 fL).	**Megaloblastic Anaemia, Liver Disease, Alcoholism, Hypothyroidism.**
Hypersegmented Neutrophils	Neutrophils with >5 lobes.	**Megaloblastic Anaemia (e.g., B12 or Folate Deficiency).**
Blasts	Large, immature cells with high nuclear-to-cytoplasmic ratio.	**Acute Leukaemia (AML, ALL), Myelodysplastic Syndromes.**
Auer Rods	Linear inclusions in myeloblasts.	**Acute Myeloid Leukaemia (AML) (especially APL subtype).**
Smudge Cells	Fragile lymphocytes appearing smudged.	**Chronic Lymphocytic Leukaemia (CLL).**
Reed-Sternberg Cells	Large binucleated cells with an "owl's eye" appearance (in lymph node aspirates).	**Hodgkin Lymphoma.**

Finding	Description	Associated Diagnoses
Toxic Granulation	Dark coarse granules in neutrophils.	**Sepsis, Severe Inflammation, Burns.**
Hypogranular Neutrophils	Neutrophils with pale cytoplasmic granules.	**Myelodysplastic Syndrome.**
Giant Platelets	Large platelets, often seen on films.	**Immune Thrombocytopenia (ITP), Bernard-Soulier Syndrome, Myeloproliferative Disorders.**
Pelger-Huët Anomaly	Neutrophils with bilobed ("dumbbell-shaped") nuclei.	**Myelodysplastic Syndrome, Hereditary Pelger-Huët Anomaly.**
Hairy Cells	Lymphocytes with cytoplasmic projections.	**Hairy Cell Leukaemia.**

Pathological White Blood Cell (WBC) Counts and Diagnostic Associations

WBC Abnormality	Description	Associated Conditions
Leukocytosis	Elevated total WBC count (>11,000/μL)	**Infections** (bacterial, viral), **Inflammation** (e.g., rheumatoid arthritis), **Myeloproliferative disorders** (CML), **Steroid use, Stress response, Tissue necrosis** (e.g., MI)
Leukopenia	Low total WBC count (<4,000/μL)	**Viral infections** (e.g., HIV, hepatitis), **Bone marrow suppression** (e.g., chemotherapy, radiation), **Autoimmune diseases** (e.g., SLE), **Aplastic anemia, Severe bacterial infections (sepsis)**
Neutrophilia	Elevated neutrophils (>7,500/μL)	**Bacterial infections, Inflammation, Stress, Myeloproliferative disorders** (e.g., CML), **Steroid use**
Neutropenia	Low neutrophils (<1,500/μL)	**Viral infections** (e.g., influenza, HIV), **Bone marrow suppression** (chemotherapy, aplastic anemia), **Autoimmune neutropenia, Severe bacterial infections** (e.g., sepsis)
Lymphocytosis	Elevated lymphocytes (>4,000/μL in adults)	**Viral infections** (e.g., EBV, CMV, hepatitis), **Chronic infections** (e.g., tuberculosis), **Lymphoproliferative disorders** (e.g., CLL)
Lymphopenia	Low lymphocytes (<1,000/μL)	**HIV/AIDS, Corticosteroid use, Autoimmune diseases** (e.g., SLE), **Bone marrow suppression, Severe infections**
Monocytosis	Elevated monocytes (>800/μL)	**Chronic infections** (e.g., tuberculosis, endocarditis), **Autoimmune diseases** (e.g., lupus, rheumatoid arthritis), **Recovery phase of infections, Myelodysplastic syndromes**

WBC Abnormality	Description	Associated Conditions
Eosinophilia	Elevated eosinophils (>500/µL)	**Allergic disorders** (asthma, atopic dermatitis), **Parasitic infections**, **Autoimmune diseases** (e.g., Churg-Strauss syndrome), **Hematologic malignancies** (e.g., Hodgkin lymphoma)
Basophilia	Elevated basophils (>200/µL)	**Myeloproliferative disorders** (e.g., CML), **Chronic inflammation** (e.g., ulcerative colitis), **Hypersensitivity reactions** (e.g., food allergies)
Blast Cells in Blood	Presence of immature WBC precursors (blasts)	**Acute leukemias** (AML, ALL), **Myelodysplastic syndromes**
Atypical Lymphocytes	Large, irregular lymphocytes with abundant cytoplasm	**Viral infections** (e.g., EBV in infectious mononucleosis, CMV), **Toxoplasmosis**

Neutropenia

Definition of Neutropenia

- **Neutropenia**: Absolute neutrophil count (ANC) <1500 cells/µL.
  - **Mild**: ANC 1000-1500 cells/µL.
  - **Moderate**: ANC 500-1000 cells/µL.
  - **Severe**: ANC <500 cells/µL.

Common Causes of Neutropenia

Category	Cause	Details
Drug-Induced	- Chemotherapy agents	Most common cause due to bone marrow suppression (e.g., cyclophosphamide, methotrexate).
	- Non-Chemotherapy drugs	Antibiotics (penicillins, sulfonamides), antipsychotics (clozapine), antithyroid drugs (methimazole), anticonvulsants (carbamazepine).
	- Immunosuppressants	Medications like azathioprine and mycophenolate mofetil.
Infections	- Viral infections	HIV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis viruses, parvovirus B19.
	- Bacterial infections	Sepsis, especially from gram-negative bacteria.
	- Other infections	Tuberculosis, malaria.
Autoimmune Disorders	- Autoimmune neutropenia	Antibodies targeting neutrophils, often isolated neutropenia.
	- Systemic lupus erythematosus (SLE)	Neutropenia as part of broader autoimmune cytopenias.
	- Rheumatoid arthritis	Felty's syndrome (triad of rheumatoid arthritis, splenomegaly, and neutropenia).

Category	Cause	Details
Bone Marrow Disorders	- Aplastic anemia	Pancytopenia with hypocellular bone marrow.
	- Myelodysplastic syndromes (MDS)	Clonal bone marrow disorder with ineffective hematopoiesis.
	- Leukemia	Particularly acute leukemias, either untreated or in relapse.
	- Lymphoma	Bone marrow infiltration suppresses neutrophil production.
Nutritional Deficiencies	- Vitamin B12 and folate deficiency	Causes pancytopenia, including neutropenia due to impaired DNA synthesis.
	- Copper deficiency	Rare cause, seen in malabsorption or post-gastric surgery cases.
Congenital and Genetic Disorders	- Cyclic neutropenia	Autosomal dominant disorder with periodic neutropenia.
	- Kostmann syndrome (severe congenital neutropenia)	Autosomal recessive disorder with severe early-onset neutropenia.
	- Shwachman-Diamond syndrome	Characterized by neutropenia, pancreatic insufficiency, and skeletal abnormalities.
Hypersplenism	- Splenic sequestration	Common in cirrhosis, portal hypertension, and hematologic diseases (e.g., lymphoma, leukemia).
Radiation Exposure	- Radiation therapy or accidental exposure	Causes bone marrow suppression leading to neutropenia.
Idiopathic Neutropenia	- Chronic idiopathic neutropenia	Often asymptomatic, commonly seen in adults, generally has a benign course.

Step-by-Step Approach to Assessing Neutropenia

Step 1: History and Clinical Assessment

- **Determine Onset and Duration**:
  - Acute or chronic neutropenia.
  - Assess for previous episodes, frequency, and duration.
- **Symptoms**:
  - Infections (recurrent bacterial/fungal), fever, mouth ulcers, sore throat.
  - Weight loss, night sweats, bone pain (if associated with malignancy or systemic disease).
- **Medical and Drug History**:
  - Recent or chronic drug use (chemotherapy, antibiotics, antipsychotics).
  - Radiation exposure, recent viral infections, autoimmune disorders.
- **Family History**:
  - History of inherited conditions (e.g., cyclic neutropenia, congenital neutropenia).

Step 2: Physical Examination

- **Signs of Infection**:
  - Oral ulcers, gingivitis, cellulitis, abscesses.
  - Signs of sepsis (fever, tachycardia, hypotension).
- **Lymphadenopathy or Splenomegaly**:
  - Suggestive of hematologic or systemic disease.
- **Skin Examination**:
  - Look for rashes, petechiae, or other signs of autoimmune involvement.

Step 3: Laboratory Evaluation

1. **Complete Blood Count (CBC)**:
   - Confirm low neutrophil count and assess for other cytopenias (anemia, thrombocytopenia).
2. **Peripheral Blood Smear**:
   - Assess for abnormal cells (e.g., blasts in leukemia, toxic granulation in infection).
3. **Absolute Neutrophil Count (ANC)**:
   - Calculate to confirm the severity of neutropenia.
4. **Liver and Renal Function Tests**:
   - Determine if there is an underlying liver or kidney dysfunction.

Step 4: Specific Testing Based on Suspected Cause

- **Viral Serologies**:
  - Test for infections like HIV, EBV, CMV, and hepatitis viruses if infection is suspected.
- **Autoimmune Markers**:
  - ANA, rheumatoid factor, anti-dsDNA for autoimmune causes such as lupus.
- **Vitamin Levels**:
  - B12 and folate deficiency can cause pancytopenia with neutropenia.
- **Bone Marrow Biopsy and Aspiration**:
  - Consider if bone marrow failure or malignancy (e.g., leukemia, myelodysplastic syndrome) is suspected.

Step 5: Drug and Toxin Evaluation

- **Drug-Induced Neutropenia**:
  - Discontinue suspect drugs if neutropenia is recent in onset and reassess counts after 1–2 weeks.
- **Assess for Toxin Exposure**:
  - Industrial exposures, alcohol, and radiation.

Step 6: Genetic Testing (If Indicated)

- **Inherited Neutropenia**:
  - Genetic testing for congenital neutropenia syndromes (e.g., cyclic neutropenia, Kostmann syndrome) if there is a relevant family history or early-onset neutropenia.

Management Based on Findings

- **Mild Neutropenia**:
  - Observation and monitoring; address any underlying cause if identified.
- **Moderate to Severe Neutropenia**:
  - **Infection Prophylaxis**: Use of prophylactic antibiotics or antifungals as needed.
  - **Granulocyte Colony-Stimulating Factor (G-CSF)**: Consider for patients with severe or chronic neutropenia at risk of infection (e.g., filgrastim).
  - **Isolation and Infection Control**: Implement for hospitalized patients with severe neutropenia.

Key Points for MRCP

1. **Detailed History**: Crucial for identifying drug-induced or infection-related neutropenia.
2. **Peripheral Blood Smear**: Helps differentiate neutropenia from other hematologic disorders.
3. **G-CSF Use**: Indicated in cases of severe neutropenia with infection risk.
4. **Bone Marrow Evaluation**: Essential if malignancy or bone marrow failure is suspected.

Leukaemoid Reaction

Definition:

- A leukaemoid reaction is an exaggerated reactive increase in the white blood cell (WBC) count (>50 × 10^9/L) resembling leukaemia but due to a benign cause, typically in response to infection, stress, or inflammation. It is characterised by increased mature and immature granulocytes in the peripheral blood.

Causes:

- **Infections**:
    - Severe bacterial infections (e.g., sepsis, pneumonia, tuberculosis).
    - Viral infections (e.g., infectious mononucleosis).
- **Inflammatory Disorders**:
    - Severe burns.
    - Rheumatoid arthritis.
    - Systemic lupus erythematosus (SLE).
- **Malignancies**:
    - Non-haematological cancers (e.g., metastatic cancers, renal cell carcinoma).
- **Stress and Physiological Conditions**:
    - Severe haemorrhage.
    - Haemolysis.
    - Post-splenectomy.
- **Drugs**:
    - Corticosteroids.
    - G-CSF administration.

Key Features:

Feature	Description
WBC Count	Markedly elevated (>50 × 10^9/L), but typically <100 × 10^9/L.
Differential	Predominantly neutrophilia with left shift (presence of bands, metamyelocytes, myelocytes).
Leukoerythroblastic Picture	Rarely includes nucleated RBCs or immature granulocytes.
Toxic Granulation	Prominent granules in neutrophils.
LAP (Leukocyte Alkaline Phosphatase) Score	Elevated (helps distinguish from chronic myeloid leukaemia (CML), which has low LAP).

Differential Diagnosis:

1. **Leukaemoid Reaction**:
   - Polyclonal WBC proliferation.
   - Normal cytogenetics.
   - LAP score: **High**.
2. **Chronic Myeloid Leukaemia (CML)**:
   - Clonal neoplastic WBC proliferation.
   - Associated with **BCR-ABL1** translocation (Philadelphia chromosome).
   - LAP score: **Low**.
   - May show basophilia and splenomegaly.

Investigations:

1. **Peripheral Blood Smear**:
   - Immature granulocytes, neutrophilia, toxic granulations.
2. **Bone Marrow Examination**:
   - Hypercellular marrow if necessary to exclude leukaemia.
3. **Cytogenetics**:
   - To exclude **Philadelphia chromosome** in suspected CML.
4. **Other Tests**:
   - Infection workup (e.g., blood cultures, serology).
   - Imaging for underlying malignancy or inflammatory cause.

Treatment:

- **Treat the underlying cause** (e.g., antibiotics for infections, steroids for inflammatory conditions).

Differentiating Chronic Myeloid Leukaemia (CML) from a Leukaemoid Reaction

Feature	Chronic Myeloid Leukaemia (CML)	Leukaemoid Reaction
Aetiology	Clonal proliferation of myeloid cells due to **BCR-ABL1 fusion** (Philadelphia chromosome).	Reactive proliferation of WBCs due to infection, inflammation, or stress.
WBC Count	Markedly elevated (often >100 × 10^9/L).	Elevated but rarely >100 × 10^9/L.
Differential Count	Increased granulocytes at all stages of maturation, including **basophilia** and eosinophilia.	Neutrophilia with a left shift (bands, myelocytes). Basophilia absent.
LAP (Leukocyte Alkaline Phosphatase) Score	**Low or absent.**	**High.**
Peripheral Blood Smear	Granulocyte precursors (myelocytes, metamyelocytes, blasts), basophilia.	Toxic granulations, neutrophilia, occasional immature cells.
Bone Marrow	Hypercellular marrow with marked granulocytic hyperplasia.	Hypercellular marrow if reactive, but no clonal abnormalities.
Cytogenetics	Presence of **Philadelphia chromosome** (t(9;22), BCR-ABL1).	Normal cytogenetics.

Feature	Chronic Myeloid Leukaemia (CML)	Leukaemoid Reaction
Basophilia	**Present**, often marked.	**Absent** or minimal.
Splenomegaly	**Marked splenomegaly** common.	Usually absent or mild.
Blast Percentage	May have <10% blasts in chronic phase.	Rarely shows blasts.
Platelet Count	May be normal, increased, or decreased depending on the phase.	Normal or mildly elevated.
Response to Infection Treatment	No response, as it is a clonal neoplastic process.	Resolves with treatment of the underlying cause.

Key Investigations to Differentiate:

1. **LAP Score:**
   - **Low in CML, high in leukaemoid reaction.**
2. **Cytogenetics and Molecular Testing:**
   - Detection of **Philadelphia chromosome** or **BCR-ABL1** confirms CML.
3. **Peripheral Blood Film:**
   - Basophilia and granulocyte precursors suggest CML.
   - Toxic granulations favour leukaemoid reaction.

- The presence of the **BCR-ABL1 fusion gene** and a low **LAP score** are the most definitive distinguishing features.

Coagulation Abnormalities and associated disorders

Coagulation Abnormality	Description	Associated Disorders
Prolonged Prothrombin Time (PT)	Elevated PT, indicating issues with the **extrinsic** and **common pathways** (factors I, II, V, VII, X)	**Liver disease**, **Vitamin K deficiency**, **Warfarin therapy**, **DIC**
Prolonged Activated Partial Thromboplastin Time (aPTT)	Elevated aPTT, reflecting problems in the **intrinsic** and **common pathways** (factors I, II, V, VIII, IX, X, XI, XII)	**Hemophilia A (Factor VIII deficiency)**, **Hemophilia B (Factor IX deficiency)**, **Von Willebrand disease**, **Liver disease**, **Heparin therapy**, **DIC**
Prolonged Thrombin Time (TT)	Elevated TT, indicating issues with **fibrinogen conversion to fibrin**	**Hypofibrinogenemia**, **DIC**, **Heparin therapy**, **Dysfibrinogenemia**
Decreased Fibrinogen Level	Low fibrinogen, suggesting consumptive or synthetic defect	**DIC**, **Liver disease**, **Afibrinogenemia**, **Severe hemorrhage**
Elevated D-Dimer	High D-dimer indicates **increased clot formation and breakdown**	**DIC**, **Pulmonary embolism**, **Deep vein thrombosis (DVT)**, **Recent surgery or trauma**
Thrombocytopenia (Low Platelet Count)	Low platelet count, causing increased bleeding risk	**ITP**, **TTP**, **DIC**, **Bone marrow suppression**, **Hypersplenism**

Coagulation Abnormality	Description	Associated Disorders
Thrombocytosis (High Platelet Count)	High platelet count, may increase clotting risk or indicate reactive state	**Myeloproliferative disorders** (e.g., essential thrombocythemia), **Post-splenectomy**, **Iron deficiency**
Positive Mixing Study (Corrected)	Correction of prolonged aPTT/PT on mixing, indicating **factor deficiency**	**Hemophilia A/B**, **Factor VII deficiency**, **Vitamin K deficiency**
Positive Mixing Study (Uncorrected)	No correction of prolonged aPTT/PT on mixing, indicating **inhibitor presence**	**Lupus anticoagulant**, **Factor inhibitors** (e.g., Factor VIII inhibitor in acquired hemophilia)
Elevated Bleeding Time	Prolonged bleeding time, indicating **platelet function abnormalities**	**Von Willebrand disease**, **Aspirin or NSAID use**, **Uremia**, **Thrombocytopathies**

A helpful way of remembering the coagulation factors of the extrinsic pathway is 3 + 7 = 10:

- **Tissue factor (factor III) and factor VII form a complex that activates factor X of the common pathway.**

A helpful way of remembering the coagulation factors of the common pathway is 10/5 = 2 × 1:

- **Factors Xa and Va form a complex that cleaves prothrombin (factor II) to thrombin (IIa).**
- **Factor IIa then cleaves fibrinogen (I) into insoluble fibrin monomers (Ia).**

Step-by-Step Approach to Assessing Anemia

1. Confirm Anemia and Severity

- **Complete Blood Count (CBC)**: Evaluate hemoglobin (Hb), hematocrit (Hct), and red blood cell (RBC) count.
- **Hemoglobin Thresholds**:
  - Anemia typically defined as Hb <13 g/dL in men and <12 g/dL in women.
- **Severity Classification**:
  - Mild: Hb 10-12 g/dL, Moderate: Hb 8-10 g/dL, Severe: Hb <8 g/dL.

2. Assess Red Cell Indices

- **Mean Corpuscular Volume (MCV)**: Determines cell size and classifies anemia as:
  - **Microcytic**: MCV <80 fL
  - **Normocytic**: MCV 80-100 fL
  - **Macrocytic**: MCV >100 fL
- **Mean Corpuscular Hemoglobin (MCH)** and **Mean Corpuscular Hemoglobin Concentration (MCHC)**: Further assess for hypochromic or normochromic cells.

3. Evaluate Reticulocyte Count

- **Reticulocyte Production Index (RPI)**: Determines if the bone marrow response is adequate.
  - **High Reticulocyte Count**: Indicates increased RBC production due to acute blood loss or hemolysis.
  - **Low/Normal Reticulocyte Count**: Suggests ineffective erythropoiesis (e.g., iron, B12, or folate deficiency).

4. Classification Based on MCV

MCV Category	Common Causes
Microcytic	Iron deficiency anemia, Thalassemia, Anemia of chronic disease, Sideroblastic anemia
Normocytic	Anemia of chronic disease, Acute blood loss, Hemolytic anemia, Renal disease, Aplastic anemia
Macrocytic	Vitamin B12/Folate deficiency, Liver disease, Hypothyroidism, Alcoholism, Myelodysplastic syndromes

5. Investigate Specific Causes Based on MCV

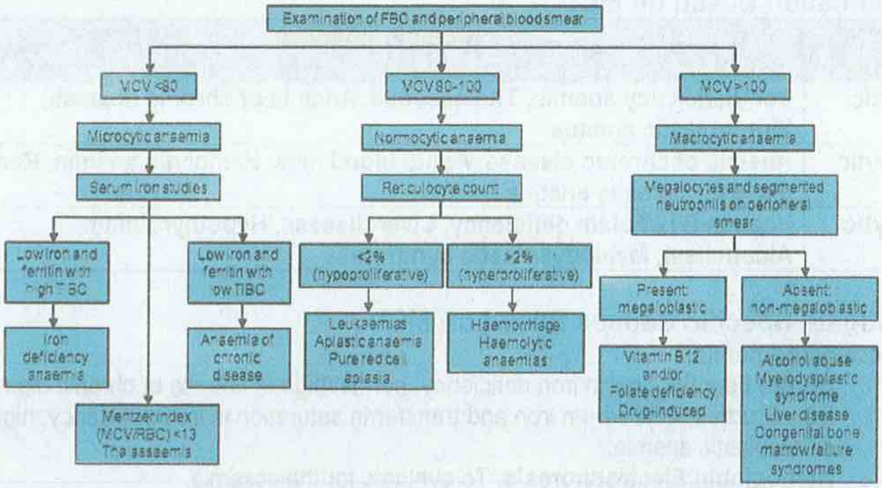
- **Microcytic Anemia**:
  - **Serum Ferritin**: Low in iron deficiency, normal/high in anemia of chronic disease.
  - **Iron Studies**: Low serum iron and transferrin saturation in iron deficiency; high in sideroblastic anemia.
  - **Hemoglobin Electrophoresis**: To evaluate for thalassemia.
- **Normocytic Anemia**:
  - **Reticulocyte Count**: High in hemolysis or blood loss, low in bone marrow suppression.
  - **Renal Function Tests**: To evaluate for anemia of chronic kidney disease.
  - **Bone Marrow Biopsy**: Consider if aplastic anemia or bone marrow pathology suspected.
- **Macrocytic Anemia**:
  - **Vitamin B12 and Folate Levels**: Deficiency common in macrocytic anemia.
  - **Liver Function Tests and Thyroid Profile**: To assess for liver disease or hypothyroidism.
  - **Peripheral Blood Smear**: Look for hypersegmented neutrophils in B12/folate deficiency, dysplastic features in myelodysplasia.

6. Evaluate for Hemolysis if Suspected

- **Hemolytic Workup**:
  - **LDH and Indirect Bilirubin**: Elevated in hemolysis.
  - **Haptoglobin**: Decreased in hemolytic anemia.
  - **Direct Antiglobulin Test (DAT)**: Positive in autoimmune hemolytic anemia.

7. Additional Testing Based on Clinical Context

- **Bone Marrow Biopsy**: If primary bone marrow disorders are suspected.
- **Genetic Testing**: For hereditary anemias (e.g., thalassemia, sickle cell disease).



Iron deficiency anaemia (IDA)

Definition

- A common type of anemia resulting from a lack of iron, which is essential for hemoglobin production and oxygen transport in red blood cells.

Causes

1. **Increased Iron Loss**:
   - **Gastrointestinal bleeding**: Peptic ulcer, colorectal cancer, hemorrhoids.
   - **Menstrual blood loss**: Common in premenopausal women.
   - **Frequent blood donations** or blood loss from trauma.
2. **Inadequate Iron Intake**:
   - Poor dietary intake (e.g., vegetarian or vegan diets without iron-rich foods).
   - Malnutrition or dietary restrictions.
3. **Increased Iron Requirements**:
   - Pregnancy and lactation due to higher demand for fetal development and milk production.
   - Rapid growth in children and adolescents.
4. **Malabsorption**:
   - **Gastrointestinal disorders**: Celiac disease, inflammatory bowel disease (IBD).
   - **Post-gastrointestinal surgery**: E.g., gastric bypass.

Pathophysiology

- Iron deficiency leads to insufficient hemoglobin production, resulting in smaller (microcytic), pale (hypochromic) red blood cells.
- Decreased hemoglobin reduces oxygen-carrying capacity, leading to tissue hypoxia and symptoms of anemia.

Clinical Features

- **General Symptoms**: Fatigue, pallor, weakness, dizziness.
- **Pica**: Craving for non-nutritive substances (e.g., ice, clay).
- **Glossitis**: Inflamed, sore tongue.
- **Koilonychia**: Spoon-shaped nails.
- **Angular cheilitis**: Cracks or sores at the corners of the mouth.

Diagnosis

Test	Findings in IDA
CBC	Low hemoglobin, low hematocrit, low MCV (microcytic anemia), low MCH (hypochromic anemia)
Serum Ferritin	Low (best initial test; indicates iron stores)
Serum Iron	Low
Total Iron Binding Capacity (TIBC)	High (reflects increased capacity to bind iron due to low iron levels)
Transferrin Saturation	Low

- **Peripheral Blood Smear**: Microcytic, hypochromic red blood cells; anisocytosis (variation in size) and poikilocytosis (variation in shape) may be seen.

Management

1. **Oral Iron Supplementation**:
   - **Ferrous sulfate** 325 mg once daily to three times daily.
   - Side effects include GI upset, constipation, and dark stools; can be taken with vitamin C to enhance absorption.
2. **Parenteral Iron Therapy**:
   - Indicated for patients with malabsorption, severe intolerance to oral iron, or high iron demands not met by oral supplementation.
   - Options include **iron sucrose** and **ferric carboxymaltose**.
3. **Dietary Advice**:
   - Increase intake of iron-rich foods (e.g., red meat, leafy greens, legumes).
   - Avoid consuming calcium, tea, and coffee close to iron supplementation as they inhibit iron absorption.
4. **Treat Underlying Cause**:
   - Investigate and manage sources of blood loss or malabsorption.

Monitoring

- **Reticulocyte Count**: Check 1-2 weeks after starting therapy for initial response.
- **Repeat CBC and Ferritin**: After 3 months to confirm resolution and to ensure iron stores are replenished.

Iron therapy

Oral Iron Formulations

- **Commonly Available Oral Iron Preparations**

Iron Salt	Elemental Iron %	Elemental Iron per Tablet
Ferrous sulfate	20%	65 mg per 325 mg tablet
Ferrous sulfate, exsiccated	30%	65 mg per 200 mg tablet
Ferrous gluconate	12%	38 mg per 325 mg tablet
Ferrous fumarate	33%	66 mg per 200 mg tablet

- **Absorption and Administration**
  - ⇨ **Optimal Absorption**:
    - Take iron on an **empty stomach** to improve absorption.
    - Co-administration with **ascorbic acid (vitamin C)** enhances absorption but may increase gastrointestinal (GI) side effects.

⇨ **Managing Side Effects**:
- Common GI side effects: **nausea, vomiting, constipation, black stools.**
- Taking iron with **food** can mitigate GI symptoms but reduces absorption by up to **40%**, impacting efficacy.

⇨ **Recommended Dosing in Iron Deficiency Anemia**
- **Total Daily Dose**:
  - Standard: **150–200 mg elemental iron/day** in **2–3 divided doses.**
  - Lower doses (e.g., **ferrous sulfate 325 mg once daily**) have comparable efficacy and better tolerability.

⇨ **Duration of Therapy**:
- Continue supplementation for **3–6 months.**
- Reassess for continued therapy based on clinical response and laboratory findings.

Intravenous (IV) Iron Therapy

- **Indications for IV Iron**
  - ⇨ **Inadequate response** or intolerance to oral iron.
  - ⇨ Significant ongoing blood loss.
  - ⇨ Severe malabsorption (e.g., inflammatory bowel disease, post-bariatric surgery).
  - ⇨ Severe anemia requiring rapid correction (e.g., perioperative).
- **Common IV Iron Preparations**

Preparation	Iron Content	Key Features
Iron sucrose	20 mg/mL	Lower risk of hypersensitivity reactions.
Ferric carboxymaltose	50 mg/mL	Can be given in high doses (e.g., 750–1000 mg).
Iron dextran	Variable	Requires a test dose due to hypersensitivity.

- **Dosage and Administration**
  - ⇨ Calculate total dose using the **Ganzoni formula**:
    Total iron deficit (mg)=Body weight (kg)×(15−Hb (g/dL))×2.4+Iron store (mg, typically 500)
- **Side Effects**
  - ⇨ Hypersensitivity reactions (more common with iron dextran).
  - ⇨ Local reactions (e.g., pain at the infusion site).

Key Points

1. Oral iron is first-line therapy for IDA unless contraindicated or poorly tolerated.
2. **Iron salt formulations vary in elemental iron content; accurate dosing is critical.**
3. **Taking iron on an empty stomach or with ascorbic acid maximises absorption.**
4. **Lower doses may be better tolerated with similar therapeutic outcomes.**
5. **Iron therapy requires persistence, with reassessment after 3–6 months.**
6. Intravenous iron is reserved for specific indications like malabsorption or intolerance to oral iron.

Anemia of Chronic Disease

Category	Details
Definition	Anemia associated with chronic inflammatory, infectious, or autoimmune diseases, and some malignancies.
Pathophysiology	- Inflammatory cytokines (e.g., IL-6) increase **hepcidin** production, reducing iron availability for erythropoiesis. - Decreased erythropoietin (EPO) production and responsiveness lead to reduced red blood cell production. - Shortened RBC lifespan due to inflammation.
Common Causes	- Chronic infections (e.g., tuberculosis, HIV) - Chronic inflammatory diseases (e.g., rheumatoid arthritis, IBD) - Malignancies - Chronic kidney disease
Red Cell Indices	- **MCV**: Usually normocytic, but can be mildly microcytic - **MCH**: Normochromic
Laboratory Findings	- **Serum Iron**: Low - **Ferritin**: Normal or elevated (reflects inflammation, not iron deficiency) - **TIBC**: Low (reduced iron-binding capacity) - **Transferrin Saturation**: Low
Differentiation from Iron Deficiency Anemia (IDA)	- **Ferritin** is elevated in ACD (low in IDA) - **TIBC** is low in ACD (high in IDA) - **Transferrin Saturation** is low in both conditions
Management	- **Treat underlying disease**: Essential to improve anemia - **Iron supplementation**: Usually not effective unless combined with erythropoietin in select cases (e.g., chronic kidney disease) - **Erythropoiesis-stimulating agents (ESAs)**: Used in CKD-related anemia

Thalassaemias

Definition

- **Thalassemias** are a group of inherited blood disorders characterized by **reduced or absent synthesis of globin chains** (alpha or beta) in hemoglobin, leading to **ineffective erythropoiesis** and **hemolysis**.

Types of Thalassemia

Type	Globin Chain Affected	Main Forms	Prevalence
Alpha Thalassemia	Reduced or absent synthesis of alpha-globin chains	Silent carrier, Alpha-thalassemia trait, Hemoglobin H disease, Hydrops fetalis	More common in Southeast Asia, Africa
Beta Thalassemia	Reduced or absent synthesis of beta-globin chains	Beta-thalassemia minor, Beta-thalassemia intermedia, Beta-thalassemia major (Cooley's anemia)	More common in Mediterranean, Middle Eastern, and Asian populations

Alpha Thalassemia Types

Type	Genetic Defect	Clinical Features	Diagnosis
Silent Carrier	1 alpha gene deletion	Asymptomatic, mild microcytosis	Normal hemoglobin electrophoresis; mild microcytosis on CBC
Alpha-thalassemia Trait	2 alpha gene deletions	Mild microcytic anemia, typically asymptomatic	Mildly low MCV and MCH, normal to mildly reduced hemoglobin
Hemoglobin H Disease	3 alpha gene deletions	Moderate to severe anemia, hepatosplenomegaly	Hemoglobin electrophoresis shows **Hb H** (beta tetramers); target cells on blood smear
Hydrops Fetalis	4 alpha gene deletions (no alpha chains)	Severe fetal anemia, hydrops fetalis, fatal at birth	Diagnosis by prenatal testing (no viable hemoglobin in fetus)

Beta Thalassemia Types

Type	Genetic Defect	Clinical Features	Diagnosis
Beta-thalassemia Minor	1 beta gene mutation (heterozygous)	Mild microcytic anemia, usually asymptomatic	Mild anemia, increased HbA2 on hemoglobin electrophoresis
Beta-thalassemia Intermedia	Variable beta gene mutations (milder homozygous or compound heterozygous)	Moderate anemia, may require transfusions in times of stress	Moderate anemia, elevated HbA2 and HbF
Beta-thalassemia Major (Cooley's anemia)	2 beta gene mutations (homozygous)	Severe anemia, growth retardation, hepatosplenomegaly, bone deformities	Severe microcytic anemia, elevated HbF and HbA2; diagnosed by electrophoresis and genetic testing

Clinical Features of Thalassemia

- **Mild forms** (Silent Carrier, Minor): Often asymptomatic or have mild anemia.
- **Moderate forms** (Hemoglobin H disease, Beta-thalassemia intermedia): Anemia, splenomegaly, mild symptoms that worsen during stress.
- **Severe forms** (Hydrops fetalis, Beta-thalassemia major): Severe anemia, need for regular blood transfusions, iron overload, bone deformities, growth delay.

General Diagnostic Approach

1. **Complete Blood Count (CBC)**: Shows microcytic, hypochromic anemia with low MCV and MCH in most cases.
2. **Peripheral Blood Smear**: Reveals target cells, poikilocytosis, and anisocytosis.
3. **Hemoglobin Electrophoresis**: Used to identify abnormal hemoglobin variants and determine the levels of HbA, HbA2, and HbF.
4. **Genetic Testing**: Confirms diagnosis, especially for prenatal and family screening.

Alpha Thalassemia Diagnostic Criteria

Type	CBC Findings	Peripheral Smear	Hemoglobin Electrophoresis	Genetic Testing
Silent Carrier	Normal to mild microcytosis	Mild microcytosis, no significant findings	Normal (no significant Hb variants detected)	1 alpha gene deletion
Alpha-thalassemia Trait	Mild microcytic anemia, low MCV and MCH	Mild target cells, mild hypochromia	Normal or slightly reduced HbA, increased Hb Bart's in newborns	2 alpha gene deletions
Hemoglobin H Disease	Moderate microcytic anemia	Target cells, Heinz bodies (Hb H inclusions)	Hb H (beta tetramers), low HbA	3 alpha gene deletions
Hydrops Fetalis	Severe anemia (incompatible with life)	Target cells, anisopoikilocytosis	Hb Bart's (gamma tetramers), absence of HbA, HbF	4 alpha gene deletions

Beta Thalassemia Diagnostic Criteria

Type	CBC Findings	Peripheral Smear	Hemoglobin Electrophoresis	Genetic Testing
Beta-thalassemia Minor	Mild microcytic anemia, low MCV and MCH	Mild target cells, microcytosis	Elevated HbA2 (>3.5%), normal to slightly increased HbF	Heterozygous mutation in 1 beta gene
Beta-thalassemia Intermedia	Moderate microcytic anemia, low MCV and MCH	Target cells, anisopoikilocytosis	Elevated HbA2, increased HbF	Compound heterozygous or milder homozygous mutation
Beta-thalassemia Major	Severe microcytic anemia, very low MCV and MCH	Target cells, nucleated RBCs, marked hypochromia	Markedly elevated HbF, increased HbA2, low or absent HbA	Homozygous or severe mutations in both beta genes

Disproportionate microcytic anaemia - think beta-thalassaemia trait

Management

1. **Mild Cases (Minor/Carrier)**: Usually require no treatment.
2. **Moderate to Severe Cases (Intermedia, Major)**:
   - **Regular Blood Transfusions**: To maintain hemoglobin levels, especially in beta-thalassemia major.
   - **Iron Chelation Therapy**: To prevent iron overload from transfusions.
   - **Splenectomy**: Considered in cases with severe splenomegaly.
   - **Folic Acid Supplementation**: Supports erythropoiesis.
   - **Bone Marrow Transplantation**: Potential curative option in severe cases.

Pure Red Cell Aplasia (PRCA)

Definition

- PRCA is a rare hematologic disorder characterized by **selective absence of red blood cell (RBC) precursors** in the bone marrow, leading to **severe anemia** with preserved white blood cells and platelets.

Causes

1. **Primary (Idiopathic)**:
   - No identifiable cause, may have an autoimmune basis.
2. **Secondary**:
   - **Thymoma**: Often associated with PRCA; removal may improve symptoms.
   - **Autoimmune Disorders**: Systemic lupus erythematosus (SLE), rheumatoid arthritis.
   - **Infections**: Parvovirus B19 (common in immunocompromised), HIV, hepatitis.
   - **Medications**: Certain drugs (e.g., phenytoin, azathioprine) and chemotherapy.
   - **Malignancies**: Leukemias, lymphomas.

Pathophysiology

- PRCA results from an **immune-mediated attack** or **direct suppression** of erythroid progenitors in the bone marrow, leading to decreased RBC production and anemia.

Clinical Features

- **Symptoms of Anemia**: Fatigue, pallor, weakness, shortness of breath.
- **Associated Conditions**: Symptoms related to underlying causes (e.g., thymoma, autoimmune disease).
- **No Signs of Leukopenia or Thrombocytopenia**: Only RBCs are affected.

Diagnosis

Test	Findings in PRCA
Complete Blood Count (CBC)	Low hemoglobin (severe anemia), normal WBC and platelet counts
Reticulocyte Count	Very low, reflecting reduced RBC production
Bone Marrow Biopsy	Absence of erythroid precursors; normal myeloid and megakaryocytic lineages
Parvovirus B19 PCR	Positive in cases due to parvovirus infection
Additional Tests	Chest imaging (to check for thymoma), autoimmune panel if autoimmune disease is suspected

Management

1. **Treat Underlying Cause**:
   - **Thymectomy** if associated with thymoma.
   - **Discontinue causative medications**.
   - **Antiviral therapy** in parvovirus B19 infections in immunocompromised patients.
2. **Immunosuppressive Therapy**:
   - **Corticosteroids**: Often first-line for idiopathic or autoimmune-related PRCA.
   - **Other Immunosuppressants**: Cyclosporine, azathioprine, or cyclophosphamide for steroid-refractory cases.
3. **Supportive Therapy**:
   - **Transfusions** as needed for severe anemia.
   - **IV Immunoglobulin (IVIG)**: Considered in PRCA due to parvovirus in immunocompromised patients.

Key Points for MRCP

1. PRCA is marked by **severe anemia with very low reticulocyte count and normal WBC/platelets.**
2. **Bone marrow biopsy** is essential to confirm the absence of erythroid precursors.
3. **Treat underlying causes** (e.g., thymoma, infections) and use immunosuppressive therapy for idiopathic cases.

Macrocytic anaemia

Definition

- Macrocytic anemia is characterized by **enlarged red blood cells (RBCs)** with a **mean corpuscular volume (MCV) >100 fL.**

Types of Macrocytic Anemia

Type	Description	Common Causes
Megaloblastic Anemia	Caused by impaired DNA synthesis, leading to large, immature RBCs (megaloblasts)	**Vitamin B12 deficiency, Folate deficiency, Drug-induced** (e.g., methotrexate, hydroxyurea), **MDS** (Myelodysplastic syndrome)
Non-Megaloblastic Anemia	Large RBCs not due to DNA synthesis impairment	**Liver disease, Alcoholism, Hypothyroidism, Reticulocytosis** (in response to hemolysis or blood loss)

Causes of Macrocytic Anemia

1. **Vitamin B12 Deficiency**:
   - Causes: Pernicious anemia, malabsorption (e.g., gastric surgery, Crohn's disease), vegetarian diet.
   - Pathophysiology: Impairs DNA synthesis, leading to ineffective erythropoiesis and megaloblastic changes.
2. **Folate Deficiency**:
   - Causes: Poor diet, alcoholism, malabsorption (e.g., celiac disease), increased demand (e.g., pregnancy).
   - Pathophysiology: Similar to B12 deficiency, affecting DNA synthesis.
3. **Medications**:
   - Drugs that impair DNA synthesis (e.g., methotrexate, hydroxyurea, anticonvulsants) can cause macrocytosis.
4. **Liver Disease**:
   - Liver dysfunction leads to altered lipid metabolism, affecting RBC membrane structure and causing macrocytosis.
5. **Alcoholism**:
   - Direct toxic effect on bone marrow and often associated with folate deficiency.
6. **Hypothyroidism**:
   - Decreased metabolism affects RBC maturation, leading to macrocytosis.
7. **Myelodysplastic Syndromes (MDS)**:
   - Bone marrow disorder leading to abnormal RBC maturation, common in elderly.

Clinical Features

- **Symptoms of Anemia**: Fatigue, pallor, weakness, shortness of breath.
- **Vitamin B12 Deficiency Symptoms**:
  - **Neurological Symptoms**: Numbness, tingling, gait instability, cognitive changes.
- **Folate Deficiency Symptoms**:
  - Symptoms are similar to B12 deficiency but without neurological findings.

Diagnosis

Test	Findings in Macrocytic Anemia
Complete Blood Count (CBC)	High MCV (>100 fL), low hemoglobin (anemia)
Peripheral Blood Smear	**Megaloblastic anemia**: Macrocytes, hypersegmented neutrophils **Non-megaloblastic**: Round macrocytes
Vitamin B12 and Folate Levels	Low in cases of B12 or folate deficiency
Liver Function Tests	Elevated in liver disease-related macrocytic anemia
Thyroid Function Tests	Low thyroid levels in hypothyroidism
Bone Marrow Biopsy	Megaloblastic changes in B12 or folate deficiency; abnormal maturation in MDS

Management

1. **Vitamin B12 Deficiency**:
   - **Oral or IM Vitamin B12**: IM route for pernicious anemia or severe deficiency (e.g., 1 mg every day for 1 week, then weekly for 1 month, then monthly).
2. **Folate Deficiency**:
   - **Oral Folate Supplements**: 1-5 mg daily until deficiency is corrected and risk factors are managed.
3. **Treat Underlying Conditions**:
   - **Liver Disease**: Manage underlying liver disorder.
   - **Alcohol Cessation**: Essential for recovery in alcohol-induced macrocytosis.
   - **Hypothyroidism**: Thyroid hormone replacement therapy.
4. **Myelodysplastic Syndromes (MDS)**:
   - Managed according to disease severity, may include supportive care, transfusions, or chemotherapy for severe cases.

Key Points for MRCP Candidates

1. **Megaloblastic vs. Non-megaloblastic**: Megaloblastic anemia has impaired DNA synthesis (e.g., B12, folate deficiency); non-megaloblastic causes are often linked to liver disease, alcoholism, or hypothyroidism.
2. **B12 deficiency** has **neurological symptoms**; folate deficiency does not.
3. **Hypersegmented neutrophils** on a smear are a hallmark of **megaloblastic anemia**.

Pernicious anaemia

Definition

- An autoimmune disorder leading to **vitamin B12 deficiency** due to **loss of intrinsic factor (IF)**, which is essential for vitamin B12 absorption.

Pathophysiology

- **Autoimmune destruction** of gastric parietal cells leads to a lack of intrinsic factor production.
- Without intrinsic factor, vitamin B12 cannot be absorbed in the ileum, leading to deficiency.
- Associated with **autoimmune gastritis**, which can lead to achlorhydria (low stomach acid).

Causes and Risk Factors

1. **Genetic Predisposition**: Family history of autoimmune diseases.
2. **Autoimmune Disorders**: Often coexists with other autoimmune conditions, such as type 1 diabetes, Hashimoto's thyroiditis, and vitiligo.
3. **Age**: More common in older adults.
4. **Other Risk Factors**: Higher incidence in individuals of Northern European descent.

Clinical Features

- **Anemia Symptoms**: Fatigue, pallor, weakness, shortness of breath.
- **Neurological Symptoms**: Tingling, numbness, difficulty walking, memory impairment, mood changes.
- **Glossitis**: Smooth, sore, swollen tongue.
- **Gastrointestinal Symptoms**: Mild jaundice, anorexia, weight loss.

Diagnosis

Test	Findings in Pernicious Anemia
Complete Blood Count (CBC)	Macrocytic anemia (high MCV), low hemoglobin, low hematocrit.
Peripheral Blood Smear	Macrocytosis, hypersegmented neutrophils, possible ovalocytes.
Serum Vitamin B12	Low vitamin B12 levels.
Intrinsic Factor Antibodies	Positive in approximately 50-70% of cases; specific to pernicious anemia.
Parietal Cell Antibodies	Present in 85-90% of cases but less specific; can also be found in other autoimmune disorders.
Serum Methylmalonic Acid (MMA) and Homocysteine	Elevated in B12 deficiency; useful in early diagnosis.
Gastric Analysis	Reduced gastric acid (achlorhydria) due to parietal cell loss.

Management

1. **Vitamin B12 Replacement**:
   - **Intramuscular (IM) B12 Injections**: 1 mg daily for 1 week, then weekly for 1 month, followed by monthly maintenance doses.
   - **Oral B12 Supplements**: Possible for maintenance in some patients, but IM route is preferred, especially in severe deficiency.
2. **Lifelong Treatment**:
   - Pernicious anemia requires lifelong B12 supplementation due to the irreversible loss of intrinsic factor.
3. **Monitor Response**:
   - **Reticulocyte Count**: Should increase within 1-2 weeks, indicating a response.
   - **Neurological Symptoms**: May take longer to improve, but early intervention is key to prevent irreversible damage.

Complications

- **Neurological Damage**: If untreated, vitamin B12 deficiency can lead to irreversible nerve damage and subacute combined degeneration of the spinal cord.
- **Increased Gastric Cancer Risk**: Autoimmune gastritis in pernicious anemia is associated with a higher risk of gastric carcinoma.
- **Other Autoimmune Conditions**: Patients may have or develop additional autoimmune diseases (e.g., thyroid disorders).

Key Points for MRCP Candidates

1. **Macrocytic anemia with neurological symptoms** is suggestive of pernicious anemia.
2. **Intrinsic factor antibodies** are diagnostic but may not be present in all cases; parietal cell antibodies can support the diagnosis.
3. **IM vitamin B12** is the mainstay of treatment, and lifelong supplementation is required.
4. Early diagnosis and treatment are crucial to prevent **irreversible neurological complications**.

Vitamin B12 (Cobalamin) Deficiency

Category	Details
Definition	A condition characterized by low levels of vitamin B12, essential for DNA synthesis, neurological function, and RBC formation.
Causes	- **Pernicious Anemia**: Autoimmune destruction of gastric parietal cells, leading to loss of intrinsic factor. - **Dietary Deficiency**: Vegetarian or vegan diet without B12 supplementation. - **Malabsorption**: Gastric surgery, Crohn's disease, celiac disease, atrophic gastritis. - **Medications**: Metformin, proton pump inhibitors (PPIs).
Pathophysiology	B12 is required for DNA synthesis and myelin formation. Deficiency leads to impaired erythropoiesis (megaloblastic anemia) and demyelination of nerves.
Clinical Features	- **Anemia Symptoms**: Fatigue, pallor, weakness, shortness of breath. - **Neurological Symptoms**: Paresthesias, numbness, difficulty walking, memory loss. - **Glossitis**: Sore, red, swollen tongue. - **Neuropsychiatric Symptoms**: Depression, confusion, cognitive decline.
Diagnosis	- **CBC**: Macrocytic anemia (high MCV), low hemoglobin. - **Peripheral Blood Smear**: Hypersegmented neutrophils, macrocytosis. - **Serum B12 Levels**: Low (<200 pg/mL). - **Methylmalonic Acid (MMA) and Homocysteine Levels**: Elevated (more sensitive for early deficiency). - **Intrinsic Factor Antibodies**: Positive in pernicious anemia.
Management	- **Oral B12 Supplements**: For mild deficiency or dietary insufficiency. - **Intramuscular (IM) B12**: 1 mg daily for 1 week, then weekly for 1 month, followed by monthly maintenance doses (used for severe deficiency or pernicious anemia). - **Dietary Changes**: Include B12-rich foods (meat, fish, dairy, fortified cereals).
Monitoring	- **Reticulocyte Count**: Response seen within 1-2 weeks of treatment. - **CBC and B12 Levels**: Recheck after 2-3 months to confirm improvement. - **Neurological Symptoms**: May take months to fully recover, if reversible.

Category	Details
Complications	- **Irreversible Neuropathy**: If deficiency persists without treatment. - **Subacute Combined Degeneration**: Affects spinal cord, causing permanent neurological damage.
Key Points for MRCP	- B12 deficiency is a **common cause of macrocytic anemia** with neurological symptoms. - **Hypersegmented neutrophils** are a classic finding. - Early treatment is crucial to prevent irreversible neurological damage. - Pernicious anemia requires lifelong **IM B12 therapy**.

Vitamin B6 (pyridoxine) deficiency

Sources	Meats, whole grains, vegetables, and nuts
Functions	▪ Immune function ▪ Heme synthesis ▪ Neurotransmitter synthesis ▪ Glycogenolysis
Causes	▪ Malnutrition ▪ Alcohol drinking ▪ Chronic renal failure, Chronic hepatitis ▪ Drugs: hydralazine: isoniazid, oral contraceptives, and levodopa/carbidopa
Features	▪ Skin: dermatitis, glossitis, stomatitis ▪ Neuro: irritability, confusion, depression, seizure and peripheral neuropathy ▪ Blood: microcytic anaemia
Treatment	▪ Deficiency: IM, IV: 10 to 20 mg/day for 3 weeks, (oral: 25 to 100 mg daily for 1 to 2 weeks) then 2 to 5 mg/day ▪ Seizure: IV: 100 mg as a single dose; repeat as needed at 5- to 10-minute intervals up to a total dose of 500 mg

Sickle cell disease (SCD)

Definition

- Sickle cell disease is an **inherited hemoglobinopathy** characterized by the production of abnormal hemoglobin S (HbS), leading to **sickle-shaped red blood cells** under low oxygen conditions, causing hemolysis and vaso-occlusive episodes.

Genetics

- **Autosomal recessive disorder** caused by a point mutation in the beta-globin gene (HBB) on chromosome 11.
- **Homozygous (HbSS)**: Sickle cell anemia (most severe form).
- **Heterozygous (HbAS)**: Sickle cell trait (carrier state, generally asymptomatic).

Pathophysiology

- **HbS Polymerization**: In low oxygen, HbS polymerizes, distorting RBCs into a sickle shape.
- **Vaso-occlusion**: Sickle cells adhere to endothelium, causing blockages in small blood vessels, leading to ischemia and infarction.
- **Hemolysis**: Sickled cells are fragile and easily destroyed, causing chronic hemolytic anemia.

Clinical Features

- **Chronic Hemolytic Anemia**: Fatigue, pallor, jaundice, elevated bilirubin, gallstones.
- **Vaso-occlusive Crises (Pain Crises)**: Episodes of severe pain due to microvascular occlusion, commonly affecting bones, chest, and abdomen.
- **Acute Chest Syndrome**: Sudden onset of chest pain, fever, and hypoxia; can be life-threatening.
- **Splenic Sequestration**: Sudden pooling of blood in the spleen, causing hypovolemic shock (more common in children).
- **Aplastic Crisis**: Temporary cessation of RBC production, often triggered by parvovirus B19 infection.
- **Infections**: Increased risk due to functional asplenia; susceptibility to encapsulated bacteria (e.g., Streptococcus pneumoniae).
- **Other Complications**: Stroke, avascular necrosis, leg ulcers, priapism, renal dysfunction.

Diagnosis

Test	Findings in SCD
Hemoglobin Electrophoresis	Presence of HbS; confirms diagnosis and differentiates from other hemoglobinopathies
Complete Blood Count (CBC)	Low hemoglobin, elevated reticulocyte count due to hemolysis
Peripheral Blood Smear	Sickled RBCs, Howell-Jolly bodies (if asplenic), target cells
Bilirubin and LDH	Elevated due to hemolysis
Screening in Newborns	Early detection through newborn screening programs, particularly in high-prevalence areas

Management

1. **Preventive Care**:
   - **Hydroxyurea**: Increases fetal hemoglobin (HbF) production, reducing sickling episodes and pain crises.
   - **Folic Acid Supplementation**: Supports increased RBC turnover.
   - **Vaccination**: Pneumococcal, Haemophilus influenzae type B, meningococcal vaccines due to increased infection risk.
   - **Penicillin Prophylaxis**: Daily prophylactic antibiotics in young children to prevent infections.
2. **Management of Acute Complications**:
   - **Vaso-occlusive Crisis**: Pain control (NSAIDs, opioids), hydration, and oxygen as needed.
   - **Acute Chest Syndrome**: Oxygen, pain control, antibiotics, bronchodilators, and possibly exchange transfusion in severe cases.
   - **Blood Transfusions**: For severe anemia, acute chest syndrome, and stroke prevention.

3. **Curative Treatment**:
   - **Stem Cell Transplantation**: The only curative treatment; suitable for selected patients with matched donors.

Complications

Complication	Description
Infections	Increased risk of bacterial infections due to functional asplenia
Stroke	Common in children; requires regular screening and possibly chronic transfusion therapy for prevention
Acute Chest Syndrome	A leading cause of morbidity and mortality; presents with chest pain, hypoxia, fever
Avascular Necrosis	Bone infarction leading to joint damage, often affecting the femoral head
Renal Dysfunction	Hematuria, hyposthenuria, glomerulopathy due to sickling in renal medulla
Pulmonary Hypertension	Chronic complication with significant morbidity and mortality

Key Points for MRCP Candidates

1. **Hemoglobin Electrophoresis** is the gold standard for diagnosing SCD.
2. **Hydroxyurea** is the mainstay of treatment to reduce vaso-occlusive episodes and complications.
3. **Acute Chest Syndrome** and **infections** are life-threatening complications requiring prompt treatment.
4. **Stem cell transplantation** offers a potential cure but is limited by donor availability and patient eligibility.

Sideroblastic anaemia

Definition

- Sideroblastic anemia is a **disorder of ineffective erythropoiesis** characterized by the presence of **ringed sideroblasts** in the bone marrow, where iron accumulates in mitochondria around the nucleus due to defective incorporation into hemoglobin.

Types

Type	Description
Congenital Sideroblastic Anemia	Genetic form, usually due to mutations in ALAS2 (X-linked sideroblastic anemia), affecting heme synthesis.
Acquired Sideroblastic Anemia	More common; often secondary to toxins, drugs, or underlying diseases.
Refractory Sideroblastic Anemia	A type of myelodysplastic syndrome with ineffective erythropoiesis and ringed sideroblasts.

Causes

1. **Congenital (Genetic) Causes**:
   - **X-linked**: Mutations in ALAS2 gene, affecting delta-aminolevulinic acid synthase enzyme.
   - **Mitochondrial Disorders**: Rarely associated with mitochondrial mutations.

2. **Acquired Causes**:
   - **Alcoholism**: Alcohol interferes with heme synthesis.
   - **Lead Poisoning**: Inhibits enzymes in the heme pathway.
   - **Medications**: Isoniazid, chloramphenicol, and linezolid can induce sideroblastic anemia.
   - **Nutritional Deficiency**: Vitamin B6 (pyridoxine) deficiency is essential for heme synthesis.
   - **Copper Deficiency**: Rare but can cause sideroblastic changes.
3. **Refractory Anemia with Ringed Sideroblasts (RARS)**:
   - A myelodysplastic syndrome (MDS) subtype associated with ringed sideroblasts.

Pathophysiology

- Defective **heme synthesis** leads to abnormal iron accumulation within mitochondria around the nucleus of erythroblasts.
- Results in **ineffective erythropoiesis** and formation of ringed sideroblasts in the bone marrow.

Clinical Features

- **Symptoms of Anemia**: Fatigue, pallor, weakness, dyspnea.
- **Iron Overload Symptoms** (in severe cases): Liver damage, heart dysfunction, diabetes due to excess iron deposition.

Diagnosis

Test	Findings in Sideroblastic Anemia
Complete Blood Count (CBC)	Microcytic or normocytic anemia; low hemoglobin
Peripheral Blood Smear	Hypochromic, microcytic cells; anisocytosis, poikilocytosis
Iron Studies	High serum iron, high ferritin, and low TIBC
Bone Marrow Biopsy	Presence of **ringed sideroblasts** (erythroblasts with iron-laden mitochondria around the nucleus)
Genetic Testing	For congenital cases (e.g., ALAS2 mutations)
Lead Levels	Measured if lead poisoning is suspected

Management

1. **Treat Underlying Cause**:
   - **Alcohol Abstinence**: For alcohol-induced sideroblastic anemia.
   - **Remove Offending Drugs**: Discontinue medications if they are the cause.
   - **Vitamin B6 (Pyridoxine) Supplementation**: Often effective, especially in congenital or nutritional deficiency cases.
2. **Iron Chelation Therapy**:
   - For cases with iron overload (e.g., deferoxamine, deferasirox) to prevent organ damage.
3. **Supportive Care**:
   - **Blood Transfusions**: For severe anemia, though this may exacerbate iron overload.
   - **Folic Acid Supplementation**: To support erythropoiesis.
4. **Bone Marrow Transplantation**:
   - Considered in severe congenital cases or refractory cases associated with MDS.

Key Points for MRCP

1. **Ringed sideroblasts in the bone marrow are diagnostic of sideroblastic anemia.**
2. **Pyridoxine (Vitamin B6)** is a critical treatment, especially in congenital and drug-induced cases.
3. **Iron studies show high serum iron and ferritin** with low TIBC, unlike iron deficiency anemia.
4. **Iron overload complications** are common in chronic cases, requiring monitoring and potentially iron chelation therapy.

Haemolytic anaemia

Definition

- Hemolytic anemia is a group of disorders characterized by **premature destruction of red blood cells (RBCs)**, leading to **anemia** and increased **erythropoiesis** to compensate for RBC loss.

Types of Hemolytic Anemia

Type	Description	Examples
Inherited Hemolytic Anemia	Caused by genetic defects affecting RBC membrane, hemoglobin, or enzymes.	**Hereditary spherocytosis, Sickle cell disease, Thalassemia, G6PD deficiency**
Acquired Hemolytic Anemia	Due to external factors that damage RBCs, such as immune reactions, infections, or mechanical trauma.	**Autoimmune hemolytic anemia (AIHA), Paroxysmal nocturnal hemoglobinuria (PNH), DIC**

Pathophysiology

- **Intrinsic Causes**: Defects within RBCs themselves (membrane, hemoglobin, or enzyme abnormalities).
- **Extrinsic Causes**: External factors leading to RBC destruction (immune-mediated, mechanical trauma, infections).

Clinical Features

- **General Symptoms of Anemia**: Fatigue, pallor, weakness.
- **Specific Features**:
  - **Jaundice**: Due to elevated bilirubin from RBC breakdown.
  - **Splenomegaly**: Common in chronic hemolysis as the spleen removes abnormal RBCs.
  - **Dark Urine**: From hemoglobinuria in intravascular hemolysis.

Classification and Key Examples

1. **Inherited Hemolytic Anemias**:

Subtype	Description	Key Features
Hereditary Spherocytosis	Membrane defect causing spherical RBCs	Jaundice, splenomegaly, spherocytes on blood smear
Sickle Cell Disease	Abnormal HbS causing sickling of RBCs	Pain crises, anemia, splenomegaly, vaso-occlusive episodes
Thalassemia	Globin chain synthesis defect (alpha or beta)	Microcytic anemia, target cells on smear, extramedullary hematopoiesis in severe cases
G6PD Deficiency	Enzyme deficiency causing oxidative damage	Triggered by oxidative stress (e.g., infections, drugs), Heinz bodies, bite cells on smear

2. **Acquired Hemolytic Anemias:**

Subtype	Description	Key Features
Autoimmune Hemolytic Anemia (AIHA)	Immune-mediated destruction of RBCs	Positive direct antiglobulin test (DAT), spherocytes, warm or cold AIHA
Paroxysmal Nocturnal Hemoglobinuria (PNH)	Stem cell defect causing complement-mediated RBC lysis	Dark urine in the morning, venous thrombosis, flow cytometry showing GPI-anchor deficiency
Microangiopathic Hemolytic Anemia (MAHA)	RBC fragmentation in small vessels due to microthrombi	Schistocytes on smear, associated with DIC, TTP, HUS, malignant hypertension
Mechanical Hemolysis	Physical damage to RBCs from prosthetic valves or circulation trauma	Schistocytes, helmet cells on smear, seen with artificial heart valves and circulatory devices

Diagnosis

Test	Findings in Hemolytic Anemia
Complete Blood Count (CBC)	Low hemoglobin, elevated reticulocyte count due to compensatory erythropoiesis
Peripheral Blood Smear	Schistocytes (fragmented cells), spherocytes, sickle cells, target cells depending on cause
LDH	Elevated due to RBC breakdown
Bilirubin	Elevated indirect (unconjugated) bilirubin from hemolysis
Haptoglobin	Decreased in intravascular hemolysis (binds free hemoglobin)
Direct Antiglobulin Test (DAT)	Positive in immune-mediated hemolytic anemia (AIHA)
Special Tests	**G6PD assay** (for G6PD deficiency), **Hemoglobin electrophoresis** (for SCD, thalassemia), **Flow cytometry** (for PNH)

Management

1. **Treat Underlying Cause:**
   - Discontinue triggering medications in drug-induced hemolysis.
   - Treat infections or autoimmune conditions.
2. **Supportive Therapy:**
   - **Folic Acid Supplementation**: To support increased erythropoiesis.
   - **Blood Transfusions**: For severe anemia.
   - **Iron Chelation**: In cases with chronic transfusions to prevent iron overload.
3. **Disease-Specific Therapies:**
   - **Corticosteroids**: First-line in warm AIHA.
   - **Hydroxyurea**: For SCD to increase fetal hemoglobin and reduce sickling.
   - **Splenectomy**: For hereditary spherocytosis and refractory cases of AIHA.
   - **Eculizumab**: For PNH to inhibit complement-mediated hemolysis.

Key Points for MRCP Candidates

1. **Elevated LDH, bilirubin, and low haptoglobin** are indicative of hemolysis.
2. **Peripheral smear findings** (e.g., spherocytes, schistocytes, sickle cells) help determine the specific type of hemolytic anemia.
3. **Direct Antiglobulin Test (DAT)** is essential for diagnosing immune-mediated hemolysis (AIHA).

Autoimmune haemolytic anaemia (AIHA)

Definition

- AIHA is a type of hemolytic anemia in which the **immune system attacks and destroys red blood cells (RBCs)**, leading to anemia. It is characterized by a positive **direct antiglobulin test (DAT)** or Coombs test.

Types of AIHA

Type	Mechanism	Optimal Temperature	Associated Conditions
Warm AIHA	IgG antibodies bind to RBCs, leading to extravascular hemolysis (in spleen)	Reacts best at body temperature (37°C)	**Autoimmune diseases** (e.g., SLE, RA), **lymphoproliferative disorders** (e.g., CLL), certain medications (e.g., methyldopa)
Cold AIHA	IgM antibodies bind to RBCs in colder temperatures, activating complement and causing intravascular hemolysis	Reacts best at temperatures <37°C	**Infections** (e.g., Mycoplasma pneumoniae, EBV), **Waldenström's macroglobulinemia**, idiopathic in some cases

Pathophysiology

- **Warm AIHA**: IgG antibodies bind to RBCs at body temperature, marking them for destruction by macrophages in the spleen (extravascular hemolysis).
- **Cold AIHA**: IgM antibodies bind to RBCs at cooler temperatures, activating the complement system and leading to RBC destruction (intravascular hemolysis).

Clinical Features

- **Symptoms of Anemia**: Fatigue, pallor, weakness, dizziness, shortness of breath.
- **Jaundice**: Due to increased bilirubin from RBC breakdown.
- **Splenomegaly**: Common in warm AIHA due to RBC destruction in the spleen.
- **Acral Cyanosis**: In cold AIHA, extremities (fingers, toes) may become blue or discolored due to agglutination of RBCs at lower temperatures.

Diagnosis

Test	Findings in AIHA
Complete Blood Count (CBC)	Low hemoglobin, elevated reticulocyte count
Peripheral Blood Smear	Spherocytes (in warm AIHA), agglutination (in cold AIHA)
Direct Antiglobulin Test (DAT)	Positive in AIHA; identifies the presence of antibodies or complement on RBCs
Indirect Bilirubin	Elevated due to increased RBC breakdown
LDH	Elevated, indicating hemolysis
Haptoglobin	Decreased in intravascular hemolysis (especially in cold AIHA)
Cold Agglutinin Titer	Elevated in cold AIHA

Management

1. **Warm AIHA**:
   - **Corticosteroids**: First-line treatment (e.g., prednisone).
   - **Immunosuppressive Agents**: For steroid-refractory cases (e.g., rituximab, azathioprine).
   - **Splenectomy**: Considered for patients unresponsive to medication.
   - **Avoid Blood Transfusions**: Only if necessary and use cross-matched RBCs, as transfusions can worsen hemolysis.

2. **Cold AIHA**:
   - **Avoid Cold Exposure**: Essential to prevent hemolysis.
   - **Rituximab**: Primary treatment option.
   - **Plasmapheresis**: Considered in severe cases to remove circulating antibodies.
   - **Blood Transfusions**: Pre-warmed blood if transfusions are required.

Complications

- **Severe Anemia**: May require transfusions in life-threatening cases.
- **Thrombosis**: Increased risk in cold AIHA due to RBC clumping and intravascular hemolysis.
- **Relapse and Refractoriness**: AIHA can be recurrent or refractory to treatment.

Key Points for MRCP

1. **DAT (Coombs test)** is positive in AIHA and helps confirm the diagnosis.
2. **Warm AIHA** is treated primarily with **corticosteroids**, whereas **cold AIHA** requires **cold avoidance and rituximab**.

Hereditary spherocytosis

Epidemiology

- **Most common hereditary hemolytic anemia** in people of Northern European descent.

Aetiology

- **Autosomal dominant** disorder of the RBC cytoskeleton.
- **Mutations**: Most frequently in the **spectrin** and/or **ankyrin genes**, leading to instability of the RBC membrane.
- **RBC Shape**: Normal biconcave shape replaced by a sphere-shaped RBC, which is prone to destruction in the spleen.

Pathophysiology

- Genetic mutations lead to **defective RBC membrane proteins** (primarily spectrin and ankyrin).
- Results in decreased RBC surface area, forming **spherocytes** with reduced flexibility.
- Spherocytes become **trapped in the spleen** and are destroyed by macrophages, leading to **extravascular hemolysis** and splenomegaly.

Clinical Features

- **Anemia Symptoms**: Fatigue, pallor.
- **Jaundice**: Due to increased unconjugated bilirubin.
- **Gallstones**: Pigment stones (calcium bilirubinate), which may cause biliary colic or cholecystitis.
- **Splenomegaly**: Often with left upper quadrant pain.
- **Aplastic Crisis**: Triggered by parvovirus B19 infection.
- **Failure to Thrive** and **Congenital Abnormalities** (e.g., tower-shaped skull) in severe cases.

Complications

- **Aplastic Crisis**: Often triggered by parvovirus B19.
- **Gallstones**: Due to chronic hemolysis, may lead to cholecystitis.

Investigations

Test	Findings
CBC	Normocytic anemia, elevated RDW and MCHC.
Blood Smear	Spherocytes (RBCs with no central pallor), anisocytosis may be present.
Hemolysis Indicators	↑ Unconjugated bilirubin, ↑ LDH, ↓ haptoglobin, reticulocytosis.
Direct Antiglobulin Test (DAT)	Negative (to differentiate from autoimmune hemolytic anemia, which has a positive DAT).
EMA Binding Test	Test of choice; shows decreased binding due to RBC membrane protein deficiency.
Osmotic Fragility Test	Not recommended in routine practice; superseded by EMA test.
Ultrasound	Used to detect gallbladder complications.

Diagnosis Approach

1. **Step 1**: Perform direct antiglobulin test (DAT) to rule out autoimmune hemolytic anemia.
2. **Step 2**: If DAT is negative, confirm HS with **EMA binding test**.
3. **Advanced Testing**: In atypical cases, **osmotic gradient ektacytometry** or **cryohemolysis test** can be used.

Management

- **Supportive Care**: Folic acid supplementation.
- **Splenectomy**:
  - Indicated for symptomatic cases, best delayed until age 6 to reduce infection risk.
  - Contraindicated in hereditary stomatocytosis due to high thrombotic risk.

Glucose-6-phosphate dehydrogenase deficiency(G6PDd)

Pathophysiology

- **Genetics**: X-linked recessive inheritance, affecting mainly males, though heterozygous females may show symptoms due to X-inactivation.
- **Mechanism**: ↓G6PD → ↓NADPH → ↓glutathione → RBCs susceptible to oxidative stress → hemolysis.
- **Hemolysis**: Non-immune mediated; DAT (Coombs test) negative.

Prevalence

- Most common RBC enzyme defect, prevalent in people of **Mediterranean, African, and Chinese descent**.

Precipitating Factors for Hemolytic Crisis

1. **Infections**: Most common trigger.
2. **Drugs**: Anti-malarials (primaquine), ciprofloxacin, nitrofurantoin, sulphonamides.
3. **Foods**: Broad fava beans (favism).
4. **Other Agents**: Henna.

Features

- Often **asymptomatic** outside of crisis episodes.
- **Neonatal jaundice** commonly seen.
- **Intravascular hemolysis**: Leads to jaundice, dark urine, and potential gallstone formation.
- **Severe Hemolysis**: May cause methemoglobinemia and splenomegaly.

Diagnosis

Test	Findings in G6PD Deficiency
G6PD Enzyme Assay	Confirms diagnosis; may give false negatives during acute hemolysis (repeat after 3 months).
CBC and Hemolysis Panel	Low hemoglobin, ↑ unconjugated bilirubin, ↑ LDH, ↓ haptoglobin.
Peripheral Blood Smear	Reticulocytosis, bite cells, Heinz bodies (denatured hemoglobin).
Reticulocyte Count	Elevated 4-7 days after hemolysis onset.
Direct Antiglobulin Test (DAT)	Negative, helping distinguish from autoimmune hemolytic anemia.

Treatment

1. **Avoidance**: Key management strategy is to avoid oxidative stressors (e.g., specific drugs, fava beans).
2. **Acute Hemolysis**: Generally self-limiting, though severe cases may need blood transfusions.
3. **Methemoglobinemia**: Treated with exchange transfusion in G6PD-deficient patients; methylene blue is contraindicated as it can worsen hemolysis.

Methemoglobinemia in G6PD Deficiency

- **Definition**: Hemoglobin is oxidized to methemoglobin (Fe^{3+}), which cannot bind oxygen, leading to functional anemia.
- **Causes**: Drugs (e.g., dapsone, chloroquine), nitrites in foods, benzene derivatives.
- **Features**: Cyanosis, low SpO_2 on pulse oximetry with normal PaO_2 on ABG (saturation gap).
- **Diagnosis**: Arterial blood gas showing elevated methemoglobin levels (>10%).
- **Treatment**: Avoid methylene blue in G6PD deficiency (worsens hemolysis); use IV ascorbic acid instead.

Methemoglobinemia is suspected in a patient with unexplained cyanosis or hypoxia that does not resolve with oxygen supplementation.

Cyanosis Without Hypoxia

Definition:

Cyanosis refers to a bluish discolouration of the skin and mucous membranes due to an increased concentration of deoxygenated haemoglobin or abnormal haemoglobins. Cyanosis without hypoxia occurs when oxygen delivery and arterial oxygen levels are adequate, but other factors create a bluish appearance.

Mechanisms:

1. **Peripheral Cyanosis**:
    - Caused by reduced blood flow or increased oxygen extraction in peripheral tissues.
    - Arterial oxygenation is normal, but venous oxygen levels are low.
2. **Abnormal Haemoglobins**:
    - Conditions where haemoglobins are altered, leading to a bluish tint despite normal oxygenation.

Causes:

1. Peripheral Cyanosis:

- **Reduced Peripheral Perfusion**:
  - Shock (hypovolaemic, cardiogenic).
  - Heart failure.
  - Severe cold exposure (vasoconstriction).
- **Venous Congestion**:
  - Deep vein thrombosis (DVT) or localised venous obstruction.

2. Abnormal Haemoglobin Conditions:

- **Methaemoglobinaemia**:
  - Increased methaemoglobin (oxidised form of haemoglobin that cannot bind oxygen).
  - Causes: Drugs (e.g., dapsone, nitrates), congenital enzyme deficiencies (cytochrome b5 reductase).
- **Sulfhaemoglobinaemia**:
  - Formation of sulfhaemoglobin (irreversible oxidation of haemoglobin).
  - Causes: Exposure to sulfonamides or hydrogen sulfide.

3. Localised Cyanosis:

- **Raynaud's Phenomenon**:
  - Localised vasoconstriction causing bluish fingers or toes.
- **Peripheral Embolism**:
  - Reduced blood flow distal to an obstruction.

Clinical Features:

Feature	Peripheral Cyanosis	Abnormal Haemoglobins
Skin Temperature	Cold to touch.	Normal.
Distribution	Fingers, toes, and extremities.	Generalised or localised (e.g., lips, mucosa).
Effect of Rewarming	Improves with warming.	No improvement.
Associated Symptoms	Signs of shock, cold exposure, or vascular occlusion.	Fatigue, headache, chocolate-coloured blood (methaemoglobinaemia).

Investigations:

Test	Findings
Arterial Blood Gas (ABG)	Normal PaO_2 and oxygen saturation.
Pulse Oximetry	May be falsely low in methaemoglobinaemia.
Co-oximetry	Differentiates oxyhaemoglobin, deoxyhaemoglobin, methaemoglobin, and sulfhaemoglobin.
Complete Blood Count (CBC)	Rule out polycythaemia vera (can cause ruddy cyanotic appearance).
Peripheral Blood Smear	Heinz bodies in methaemoglobinaemia.
Enzyme Assays	Test for cytochrome b5 reductase deficiency in congenital methaemoglobinaemia.

Management:

1. Peripheral Cyanosis:

- **Address Underlying Cause**:
  - Rewarm in hypothermia.
  - Improve perfusion in shock or heart failure (e.g., fluids, inotropes).
  - Treat Raynaud's phenomenon (e.g., calcium channel blockers).

2. Methaemoglobinaemia:

- **First-Line Treatment**:
  - **Methylene Blue (1–2 mg/kg IV over 5 minutes)**:
    - Restores normal haemoglobin by reducing methaemoglobin.
- **Supportive Measures**:
  - Oxygen therapy (limited efficacy if methaemoglobin >50%).
  - Blood transfusion in severe cases.

3. Sulfhaemoglobinaemia:

- **Supportive Care**:
  - Discontinue causative agent.
  - No specific antidote; haemolysis or transfusion may be required in severe cases.

Key Points for MRCP:

1. **Peripheral cyanosis** is due to reduced local perfusion, not arterial oxygenation.
2. Always suspect **methaemoglobinaemia** or **sulfhaemoglobinaemia** when cyanosis is present with normal PaO_2 and pulse oximetry readings.
3. **Methylene blue** is the antidote for methaemoglobinaemia but is contraindicated in **G6PD deficiency** (consider ascorbic acid instead).

Paroxysmal nocturnal haemoglobinuria (PNH)

Definition

- PNH is an **acquired hematologic disorder** characterized by a triad of **hemolytic anemia, pancytopenia, and thrombosis** due to the increased susceptibility of blood cells to complement-mediated destruction.

Pathophysiology

- **Cause**: Due to a lack of **glycosyl-phosphatidyl-inositol (GPI)**, an anchor for complement-regulating proteins like **CD55 (DAF)** and **CD59 (MIRL)** on the cell membrane.
- **Effect**: Cells lacking GPI are more susceptible to complement attack, leading to **intravascular hemolysis**.
- **Hemolysis Mechanism**: Hemolysis is often exacerbated by acidosis at night, resulting in dark urine in the morning.
- **Thrombosis Mechanism**: Due to absence of CD59 on platelets, leading to increased platelet aggregation and a high risk of venous thrombosis.

Clinical Features

- **Anemia Symptoms**: Fatigue, pallor, weakness.
- **Intermittent Jaundice**: Due to hemolysis.
- **Hemoglobinuria**: Dark-colored urine, especially in the morning.
- **Abdominal Pain**: May be due to thrombosis in small mesenteric veins.

Complications

- **Thrombosis**: Often in unusual locations, such as the **Budd-Chiari syndrome** (hepatic vein thrombosis).
- **Vasoconstriction**: Causes headache and pulmonary hypertension.
- **Aplastic Anemia**: May develop in some patients.
- **Increased Risk of Acute Leukemia**: Due to bone marrow instability.

Investigations

Test	Findings in PNH
CBC	Shows **hemolytic anemia** and **pancytopenia**
Urine Dipstick	Positive for blood but no RBCs seen on microscopy, indicating intravascular hemolysis with free hemoglobin
Flow Cytometry	Gold standard: Shows **absence of CD55 and CD59** on RBCs
Ham's Test	Acid-induced hemolysis in PNH cells (now largely replaced by flow cytometry)
Coombs Test	Negative, as PNH is a non-immune hemolytic anemia

Management

1. **Supportive Care**:
   - **Blood Transfusions**: To manage anemia.
   - **Anticoagulation**: For thrombosis prevention in high-risk patients.
2. **Targeted Therapy**:
   - **Eculizumab**: A monoclonal antibody against complement protein C5, reducing intravascular hemolysis.
3. **Curative Treatment**:
   - **Stem Cell Transplantation**: The only curative treatment, although reserved for severe cases.

The triad of hemolytic anemia, pancytopenia, and thrombosis → PNH

Blood transfusion

Blood components: Indications and dosing in adults

Component (volume)	Indications and dose
Whole blood (1 unit = 500 mL)	May be appropriate when massive bleeding requires transfusion of more than 5 to 7 units of RBCs
RBCs in additive solution (1 unit = 350 mL)	▫ Anaemia, bleeding. ▫ 1 unit of RBCs →↑ Hb 1 g/dL; the increase in hematocrit 3 %.
FFP or other plasma product (1 unit = 200 to 300 mL)	▫ Bleeding or expected bleeding (eg, emergency surgery) in multiple coagulation factors deficiencies (eg, DIC, liver disease, massive transfusion, warfarin overdose). ▫ Bleeding in isolated factor deficiencies if a factor concentrate or recombinant factor is not available. ▫ Therapeutic plasma exchange in TTP (as a source of ADAMTS13). ▫ Dose is 10 to 20 mL/kg.

Component (volume)	Indications and dose
Cryoprecipitate (1 unit = 10 to 20 mL): contains Fibrinogen; factors VIII and XIII; VWF	▫ DIC. ▫ Uraemia if DDAVP (desmopressin) is ineffective. ▫ 1 unit of Cryoprecipitate per 10 kg body weight →↑ plasma fibrinogen by 50 mg/dL. ▫ Cryoprecipitate is generally provided in pools containing 5 units, and most patients receive 1 to 2 pools
Platelets (derived from whole blood or apheresis) (1 unit of apheresis platelets or a 5 to 6 unit pool of platelets from whole blood = 200 to 300 mL)	The platelet count increase from 5 to 6 units of whole blood-derived platelets or 1 unit of apheresis platelets will be approximately 30,000/microL in an average-sized adult.

Transfusion Reactions and Management

Reaction Type	Description	Management
Acute Hemolytic Reaction	ABO incompatibility causes intravascular hemolysis, fever, chills, flank pain	Stop transfusion, supportive care
Febrile Non-Hemolytic Reaction	Common, from cytokines in stored blood products; causes fever, chills	Stop transfusion, antipyretics, restart if symptoms subside
Allergic Reaction	Mild urticaria to severe anaphylaxis due to plasma proteins	Stop transfusion, antihistamines, steroids if severe
Transfusion-Related Acute Lung Injury (TRALI)	Sudden respiratory distress due to immune-mediated lung injury	Stop transfusion, supportive care with oxygen; avoid further plasma products
Transfusion-Associated Circulatory Overload (TACO)	Fluid overload causing pulmonary edema, dyspnea, hypertension	Slow infusion rate, diuretics, monitor fluid status
Delayed Hemolytic Reaction	Weeks post-transfusion, often due to undetected alloantibodies	Supportive care, monitor for anemia and renal function

Transfusion-Related Acute Lung Injury (TRALI)

Definition:

- TRALI is a serious and potentially life-threatening complication of blood transfusion characterised by acute lung injury (ALI) within 6 hours of transfusion. It involves non-cardiogenic pulmonary oedema and is considered the leading cause of transfusion-related mortality.

Pathophysiology:

- **Two-Hit Hypothesis**:
  1. **First Hit**: Patient predisposition (e.g., systemic inflammation, infection, surgery) primes the pulmonary endothelium.
  2. **Second Hit**:
     - Donor-derived **anti-HLA** or **anti-HNA (human neutrophil antigen)** antibodies activate recipient neutrophils.
     - Neutrophil activation leads to release of cytokines, proteases, and reactive oxygen species, causing endothelial damage and capillary leakage.

Risk Factors:

1. **Recipient Factors**:
   - Critically ill (e.g., ICU patients).
   - Underlying inflammation or infection.
   - Recent surgery or trauma.
2. **Donor Factors**:
   - Female donors with prior pregnancies (increased likelihood of anti-HLA antibodies).
   - Multiparous women.

Clinical Features:

1. **Timing**:
   - Symptoms develop within **6 hours** of transfusion.
2. **Symptoms**:
   - Acute dyspnoea.
   - Hypoxaemia (PaO_2/FiO_2 ratio <300 mmHg).
   - Fever.
3. **Signs**:
   - Hypotension.
   - Bilateral pulmonary infiltrates on chest X-ray (non-cardiogenic pulmonary oedema).

Diagnosis:

Clinical Diagnosis based on:

1. Acute onset of respiratory distress within 6 hours of transfusion.
2. **Non-cardiogenic pulmonary oedema**:
   - Bilateral infiltrates on imaging.
   - Normal pulmonary capillary wedge pressure (if measured).
3. Absence of other causes of ALI, such as:
   - Cardiogenic pulmonary oedema.
   - Volume overload.
   - Sepsis.

Confirmatory Testing (rarely done in acute settings):

- Detection of donor anti-HLA or anti-HNA antibodies.

Management:

1. **Supportive Care**:
   - Oxygen supplementation or mechanical ventilation in severe cases.
   - Diuretics are **not effective** as TRALI is non-cardiogenic.
2. **Stop Transfusion Immediately**:
   - Prevent further exposure to implicated products.
3. **Hemovigilance**:
   - Report to transfusion services for investigation.
   - Quarantine and testing of implicated donor products.

Prevention:

1. **Donor Screening**:
   - Exclusion of multiparous female donors for plasma products.
2. **Use of Male-Donor Plasma**:
   - Reduces risk of anti-HLA or anti-HNA antibody-mediated reactions.
3. **Leukocyte Reduction**:
   - Universal leukoreduction of blood products to reduce neutrophil activation.

Prognosis:

- Most patients recover within 48–96 hours with appropriate supportive care.
- Mortality rate: **5–10%**, higher in critically ill patients.

Key Points for MRCP:

1. **Timing is crucial**: TRALI occurs within 6 hours of transfusion.
2. Differentiate TRALI from **transfusion-associated circulatory overload (TACO)**:
   - TRALI: Non-cardiogenic, normal cardiac filling pressures.
   - TACO: Cardiogenic, raised jugular venous pressure, and evidence of fluid overload.
3. **Pulmonary infiltrates in TRALI** are due to neutrophil-mediated damage, not volume overload

Plasma Exchange (Plasmapheresis)

Definition:

- Plasma exchange (PE) is a therapeutic procedure that removes plasma containing pathogenic substances (e.g., autoantibodies, immune complexes, or toxins) from the patient's blood and replaces it with donor plasma, albumin, or saline. It is widely used in various autoimmune, haematological, and neurological conditions.

Mechanism:

- **Pathogenic Plasma Removal**:
  - Removes antibodies, immune complexes, cryoglobulins, or toxins causing disease.
- **Replenishment**:
  - Replacement with fresh frozen plasma (FFP), albumin, or saline maintains fluid balance and provides normal plasma components.

Indications:

1. Haematological:

- **Thrombotic Thrombocytopenic Purpura (TTP)**:
  - Removes ultra-large vWF multimers and autoantibodies against ADAMTS13.
- **Haemolytic Uraemic Syndrome (HUS)**:
  - Atypical HUS caused by complement dysregulation.
- **Hyperviscosity Syndrome**:
  - Seen in Waldenström macroglobulinaemia or multiple myeloma.

2. Neurological:

- **Guillain-Barré Syndrome (GBS)**:
  - Removes autoantibodies and complement.
- **Myasthenia Gravis (MG)**:
  - For acute exacerbations or pre-surgery.
- **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**.
- **Neuromyelitis Optica (NMO)**:
  - Removes pathogenic aquaporin-4 antibodies.

3. Renal:

- **Anti-GBM Disease (Goodpasture Syndrome)**:
  - Removes anti-glomerular basement membrane antibodies.
- **Rapidly Progressive Glomerulonephritis (RPGN)**:
  - In ANCA-associated vasculitis.

4. Other Autoimmune Conditions:

- **Systemic Lupus Erythematosus (SLE)**:
  - Severe lupus nephritis or catastrophic antiphospholipid syndrome.
- **Rheumatoid Vasculitis**.

5. Toxicology:

- **Drug Overdose**:
  - Drugs with high plasma protein binding (e.g., carbamazepine, theophylline).
- **Toxin Removal**:
  - E.g., lipopolysaccharides in sepsis.

Procedure:

1. **Vascular Access**:
   - Central venous catheter (preferred for large volumes).
2. **Blood Processing**:
   - Blood is drawn, separated into plasma and cellular components.
   - Plasma is discarded or treated.
   - Replacement fluid (e.g., FFP or albumin) is returned with cellular components.
3. **Frequency and Volume**:
   - Exchange ~1–1.5 times the patient's plasma volume per session.
   - Usually performed daily or every other day for a set number of sessions.

Complications:

1. **Bleeding Risk**:
   - Removal of clotting factors (e.g., fibrinogen) when FFP is not used for replacement.
2. **Hypocalcaemia**:
   - Citrate in replacement fluid chelates calcium.
3. **Hypotension**:
   - Due to fluid shifts.

4. **Infections**:
   - Central venous catheter-related.
5. **Allergic Reactions**:
   - To plasma proteins (especially with FFP).
6. **Electrolyte Imbalances**:
   - Hypokalaemia or hypomagnesaemia.

Contraindications:

- **Absolute**:
  - Haemodynamic instability.
- **Relative**:
  - Severe hypocalcaemia.
  - Active bleeding (without FFP replacement).

Key Points for MRCP:

1. **TTP** is the most common and validated indication for plasma exchange.
2. Use **FFP** for conditions needing clotting factor replacement (e.g., TTP, bleeding).
3. Monitor for **complications** like hypocalcaemia (treat with calcium gluconate).
4. Plasma exchange does not replace definitive therapies (e.g., immunosuppression in autoimmune diseases).

Deep vein thrombosis (DVT)

Risk Factors

1. **Hematological**
   - Thrombophilia (e.g., protein C/S deficiency, activated protein C resistance)
   - Polycythemia
   - Paroxysmal nocturnal hemoglobinuria
   - Hyperviscosity syndrome
2. **Autoimmune**
   - Antiphospholipid syndrome
   - Behcet's disease
3. **Drugs**
   - Combined oral contraceptives (higher risk with 3rd generation)
   - Antipsychotics (especially olanzapine)
4. **Other Conditions**
   - Homocystinuria

Diagnosis: Wells Score for DVT

Clinical Feature	Points
Active cancer (treatment ongoing or recent)	1
Paralysis or recent plaster immobilisation	1
Recently bedridden (3+ days) or major surgery	1
Localised tenderness over deep veins	1
Entire leg swollen	1
Calf swelling ≥3 cm larger than asymptomatic side	1
Pitting oedema (confined to symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis as likely as DVT	-2

Score Interpretation:
- **DVT likely**: 2+ points
- **DVT unlikely**: 1 point or less

Investigative Protocol
- **DVT likely (2+ points)**:
  - Perform proximal leg vein ultrasound within 4 hours.
  - If ultrasound delayed, perform D-dimer and start LMWH, repeat ultrasound within 24 hours if D-dimer positive.
- **DVT unlikely (1 or less)**:
  - Perform D-dimer test; if positive, arrange proximal ultrasound within 4 hours or start LMWH if delayed.

Unprovoked DVT Investigations
1. **Malignancy Screening**:
   - Physical exam, chest X-ray, blood tests (FBC, calcium, LFTs), urinalysis.
   - For patients over 40: Consider CT of the abdomen/pelvis, mammogram for women.
2. **Thrombophilia Testing**:
   - Not recommended for lifelong warfarin patients.
   - Consider in patients with family history of VTE.

Management
1. **Anticoagulation**:
   - **Initial Therapy**: Start LMWH or fondaparinux upon diagnosis.
   - **Warfarin**: Begin within 24 hours; overlap with LMWH or fondaparinux until INR >2 for 24+ hours.
   - **Duration**:
     - Provoked DVT: Warfarin for 3 months.
     - Unprovoked DVT: Consider extended therapy based on risk factors (typically 6 months).
     - Cancer patients: LMWH for 6 months.
2. **Special Populations**:
   - **Pregnancy**: Use LMWH; avoid warfarin.
   - **Active Ulcerative Colitis**: Heparinization preferred over warfarin (for surgical reversibility).
3. **Inferior Vena Cava (IVC) Filter:** For patients with contraindications to anticoagulation or recurrent DVT despite anticoagulation. Prevents emboli from reaching the lungs.
4. **Prophylaxis for Knee Replacement**:
   - LMWH or fondaparinux (start 6-12 hours post-surgery).
   - Dabigatran (start 1-4 hours post-surgery).

Pregnancy and DVT/PE
- **Hypercoagulable State**: Increased coagulation factors and venous stasis due to uterine pressure on IVC.
- **Management**: LMWH preferred; warfarin contraindicated due to teratogenicity.

Post-Thrombotic Syndrome (PTS)
- **Cause**: Chronic venous hypertension from venous outflow obstruction and insufficiency post-DVT.
- **Features**: Painful, heavy calves, pruritus, swelling, varicose veins, venous ulceration.
- **Management**: **Compression Stockings**: Below-knee stockings with 23+ mmHg ankle pressure, worn on affected leg(s) for at least 2 years, starting 1-week post-DVT if swelling is reduced.

Time of starting prophylaxis in elective knee replacement surgery:
- LMWH or fondaparinux (s/c factor X inhibitor) → should be started 6 – 12 hours after surgery
- Dabigatran (oral factor X inhibitor) → 1 – 4 hours after surgery

The next most important investigation:
- Unprovoked VTE → chest X-ray, blood tests and urinalysis
- Unprovoked VTE + family history of VTE → Thrombophilia screening

Coagulation elements in pregnancy:
- Increased → factors VII, VIII, IX, X, and XII ,fibrinogen, plasminogen, and D-dimer.
- **Decreased → factor XI and protein S.**
- Not changed → Factor II, protein C, and anti-thrombin III.

Thrombophilia

Definition

- Thrombophilia is a **predisposition to abnormal blood clot formation** (thrombosis), resulting from inherited or acquired factors that increase the risk of venous thromboembolism (VTE) or, less commonly, arterial thrombosis.

Comparison of Common Inherited Thrombophilias

Thrombophilia	Prevalence	Relative Risk of VTE	Characteristic Features
Factor V Leiden Mutation	**Most common inherited thrombophilia**; found in up to 5% of Caucasians	5-8x increased risk for heterozygotes, 50-80x for homozygotes	**Mechanism**: Mutation in Factor V gene causes resistance to activated protein C, reducing the ability to inactivate clotting factor Va, leading to increased thrombin formation.
Prothrombin Gene Mutation (G20210A)	Found in 2-3% of Caucasians; rare in other populations	2-4x increased risk of VTE	**Mechanism**: Mutation leads to elevated prothrombin levels, increasing thrombin formation and enhancing clotting.
Protein C Deficiency	Rare, estimated at 0.2-0.5% in the general population	10x increased risk for VTE	**Mechanism**: Reduced protein C activity impairs inactivation of factors Va and VIIIa, promoting clot formation. **Risk**: Often presents with unprovoked DVT or PE; **Warfarin-induced skin necrosis** is a specific complication if anticoagulation is not started with heparin.

Thrombophilia	Prevalence	Relative Risk of VTE	Characteristic Features
Protein S Deficiency	Rare, about 0.2-0.4% prevalence	5-10x increased risk of VTE	**Mechanism**: Protein S is a cofactor for protein C, so deficiency disrupts the inactivation of factors Va and VIIIa.
Antithrombin III Deficiency	Very rare; affects approximately 0.02-0.2% of the population	20x increased risk of VTE	**Mechanism**: Antithrombin inhibits thrombin and other coagulation factors (Xa, IXa), so deficiency leads to unregulated clotting. **Risk**: **Higher risk** for venous thrombosis (DVT, PE); **Heparin resistance** may occur, as heparin's effect relies on antithrombin.

Inherited thrombophilias:
- **the most common → Factor V Leiden (activated protein C resistance)**
- **the higher risk of VTE → Anti-thrombin III deficiency**

Acquired thrombophilias:
- Antiphospholipid syndrome
- Pregnancy and Oral Contraceptives
- Malignancy
- Myeloproliferative Disorders like polycythemia vera and essential thrombocythemia

Clinical Presentation
- **Venous Thromboembolism (VTE)**: Deep vein thrombosis (DVT) or pulmonary embolism (PE) is common in thrombophilia.
- **Recurrent Thrombosis**: Patients with thrombophilia often experience recurrent VTEs.
- **Unusual Clot Locations**: Thrombophilia may cause clots in atypical locations, such as cerebral, portal, or mesenteric veins.
- **Recurrent Pregnancy Loss**: Especially in antiphospholipid syndrome, with risk of miscarriage in the first trimester.

Indications of thrombophilia testing:
1. **Young age (<50 years)**: Thrombosis in absence of significant risk factors.
2. **Unprovoked/Recurrent Thrombosis**: Especially venous thromboembolism (VTE) or arterial thrombosis.
3. **Family History**: First-degree relative with thrombophilia or VTE.
4. **Unusual Sites of Thrombosis**: Cerebral, mesenteric, or portal vein thrombosis.
5. **Pregnancy Complications**: Recurrent miscarriages, fetal growth restriction, or stillbirth, especially if associated with antiphospholipid syndrome.

Thrombophilia testing

Test	Details
Screening for APS	Lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein I antibodies. Requires persistent positive antiphospholipid antibodies on two occasions 12 weeks apart.
Inherited Thrombophilia Tests	genetic testing for Factor V Leiden and prothrombin mutations, and activity levels for Protein C, Protein S, and Antithrombin deficiency.
Timing of Testing	Postpone tests until after resolution of acute thrombosis or at least 3 months off anticoagulation. Protein C, S, and antithrombin levels may be transiently reduced during acute thrombosis, pregnancy, or on anticoagulants.

Management for patients with thrombophilia

- **Short-term prophylaxis: During High-Risk Situations** (e.g., surgery, immobilization, pregnancy): Low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs)
- **Long-Term Anticoagulation**: Reserved for high-risk individuals (e.g., recurrent venous thromboembolism [VTE] or severe thrombophilia).
- **Special situation**
    - **Antiphospholipid syndrome** requires lifelong anticoagulation after a first thrombotic event.
    - **Protein C/S deficiency:** Increased risk with hormonal therapy, requiring prophylaxis in high-risk situations.
    - **Pregnancy and thrombophilia:** LMWH is the preferred agent; warfarin is contraindicated.

NICE recommend testing for thrombophilia in case of unprovoked venous thromboembolism <u>and</u> family history.

Activated protein C resistance (Factor V Leiden) is the most common inherited thrombophilia

Factor V Leiden mutation results in activated protein C resistance

Hereditary haemorrhagic telangiectasia (HHT)

Definition

- Inherited vascular disorder, Also known as **Osler-Weber-Rendu syndrome,** characterised by multiple telangiectasia over the skin and mucous membranes.

Pathophysiology

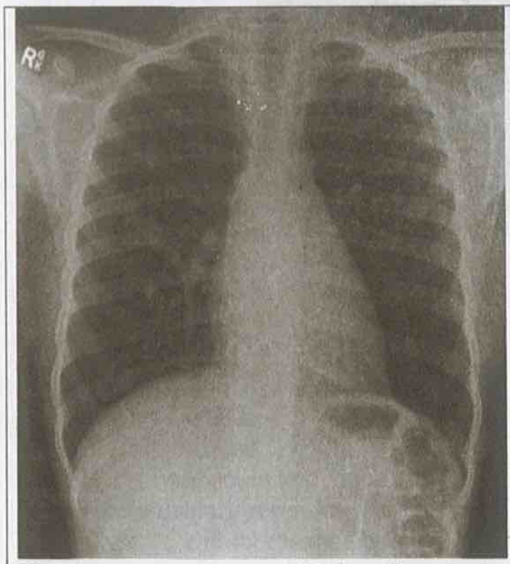
- **Autosomal dominant** Mutations in these genes, ENG (endoglin) and ALK-1 (activin receptor like kinase-1) which encode proteins expressed on vascular endothelial cells cause an imbalance in angiogenesis.

Features and complications

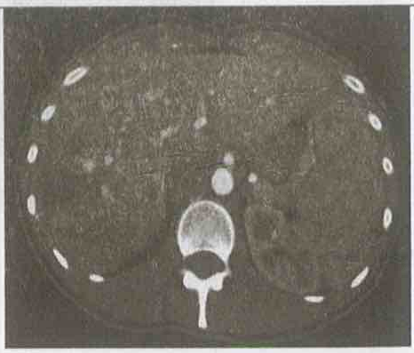
- Epistaxis **(the most common of presentation (>95%)**
- **GIT:** telangiectasias and arteriovenous malformations (AVMS) may cause chronic slow bleeding leading to iron deficiency **anemia,** may cause **acute haemorrhage**
- **Respiratory:** AVMS may cause **dyspnoea and cyanosis and paradoxical cerebral emboli.**
- **CNS:** AVMS, angiomas and aneurysms may lead to **stroke**

Diagnosis

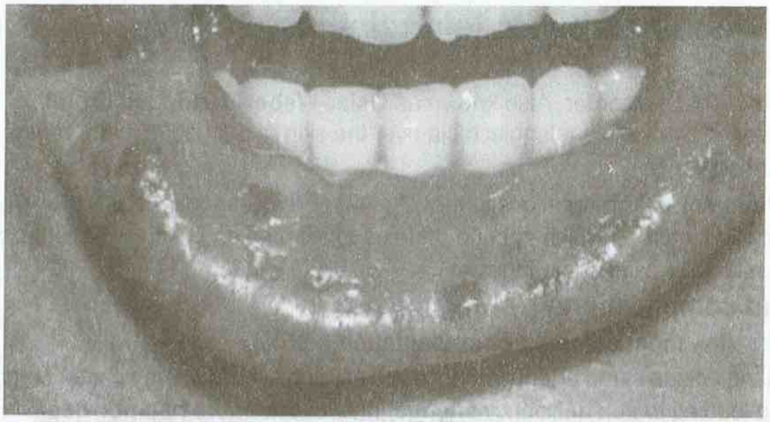
- There are 4 main **diagnostic criteria** (Curacao criteria).
    1. **Epistaxis**: spontaneous, recurrent nosebleeds
    2. **Telangiectases**: multiple at characteristic sites (lips, oral cavity, fingers, nose)
    3. **Visceral lesions:** GIT telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
    4. **Family history:** a first-degree relative with HHT
- The diagnosis is **definite** if 3 criteria are present, **suspected** with 2 criteria and **unlikely** if fewer than 2 criteria are present.



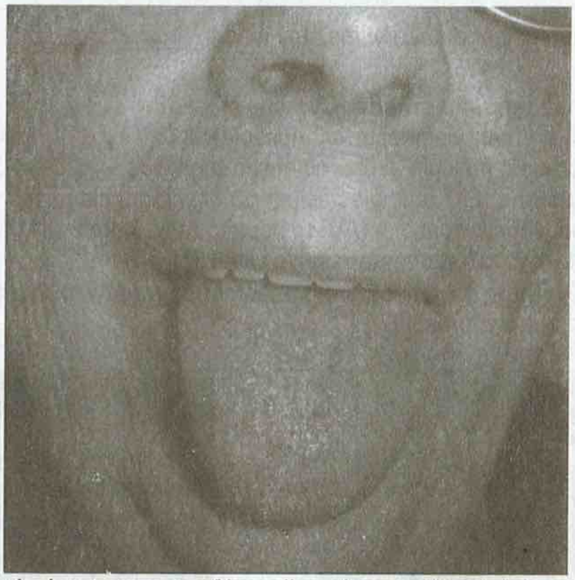
The chest x-ray shows **multiple pulmonary nodules** representing arteriovenous malformations, the largest in the right mid-zone.



The CT scan shows multiple hepatic arteriovenous malformations



Mucocutaneous telangiectasias involve the lips (HHT)



The slide shows the typical appearance of hereditary haemorrhagic telangiectasia (also known as Osler-Weber-Rendu disease)

Langerhans cell histiocytosis

Category	Details
Definition	Rare clonal disorder involving abnormal proliferation of Langerhans cells, which are specialized dendritic cells. Commonly affects children but can occur at any age.
Etiology	Exact cause unknown, but potential genetic mutations (e.g., BRAF V600E) implicated; may involve immune dysregulation.
Pathophysiology	Abnormal Langerhans cells accumulate in tissues, causing granulomatous inflammation and damage through cytokine release.
Clinical Features	**Variable, based on organ involvement** **Bone**: Painful lytic lesions, especially in skull, long bones. **Skin**: Rashes, erythematous papules. **Endocrine**: Diabetes insipidus (due to pituitary involvement). **Liver/Spleen**: Hepatosplenomegaly. **Lung**: Dyspnea, cystic lung lesions. **Lymph nodes**: Enlarged, sometimes painful lymph nodes.
Complications	Chronic pain, skeletal deformities, diabetes insipidus, chronic lung disease, and potential for multisystem organ failure if untreated.
Diagnostic Criteria	**Biopsy**: Identifies Langerhans cells with characteristic nuclear grooves, positive CD1a, S-100, and Langerin (CD207) markers. **Imaging**: X-rays for lytic bone lesions, CT/MRI for organ involvement, PET scan for multisystem disease.
Laboratory Findings	No specific lab findings, but may show elevated inflammatory markers (ESR, CRP); endocrine testing if pituitary involved.
Treatment	Depends on extent: **Single-system, low-risk**: Local therapies (surgical curettage, steroids). **Multisystem or high-risk**: Systemic chemotherapy (vinblastine, prednisone); targeted therapies (e.g., BRAF inhibitors) for refractory cases.

Myelofibrosis

Category	Details
Definition	A chronic myeloproliferative neoplasm characterized by bone marrow fibrosis, abnormal blood cell production, and extramedullary hematopoiesis, leading to splenomegaly and constitutional symptoms.
Etiology	**Primary Myelofibrosis** (idiopathic) or **Secondary Myelofibrosis** (progression from other myeloproliferative disorders, e.g., polycythemia vera or essential thrombocythemia). Associated with genetic mutations (e.g., JAK2, CALR, MPL).
Pathophysiology	Clonal proliferation of hematopoietic stem cells leads to excessive cytokine production, stimulating fibroblast proliferation and marrow fibrosis. Progressive fibrosis disrupts normal hematopoiesis, resulting in cytopenias and extramedullary hematopoiesis (primarily in the spleen and liver).

Category	Details
Clinical Features	**Constitutional Symptoms**: Fatigue, weight loss, night sweats. **Splenomegaly**: Left upper quadrant pain, early satiety. **Anemia**: Pallor, weakness. **Thrombocytosis or thrombocytopenia**: Bleeding/bruising or thrombosis.
Complications	Severe anemia, splenic infarction, portal hypertension, transformation to acute myeloid leukemia (AML) in about 10-20% of cases.
Diagnostic Criteria	Based on the 2016 WHO criteria, includes bone marrow biopsy (showing fibrosis and atypical megakaryocytes) and at least one clonal mutation (e.g., JAK2, CALR, MPL).
Laboratory Findings	**CBC**: Anemia (often macrocytic), possible leukocytosis or thrombocytosis. **Peripheral Blood Smear**: Teardrop-shaped red cells (dacrocytes), nucleated RBCs. **Bone Marrow Biopsy**: Shows increased fibrosis, typically Grade 2-3. **Molecular Testing**: JAK2 mutation (in 50-60% of cases), CALR or MPL mutations in JAK2-negative cases.
Treatment	**Supportive Care**: Blood transfusions for anemia, hydroxyurea for splenomegaly and high cell counts. **JAK Inhibitors**: Ruxolitinib is commonly used for symptomatic relief. **Allogeneic Stem Cell Transplant**: The only curative treatment, indicated for younger patients with high-risk disease. **Splenectomy**: Considered if splenomegaly is unmanageable by medical therapy.

Myelofibrosis - most common presenting symptom - lethargy

Tear-drop poikilocytes = myelofibrosis

Myelodysplastic syndrome (MDS)

Definition

- A group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, leading to blood cytopenias and potential progression to acute myeloid leukemia (AML).
- Premalignant condition, primarily affects elderly people (> 60).More common in males than in females

Etiology

- **Primary (Idiopathic)**: Often associated with aging, genetic mutations.
- **Secondary (Therapy-Related)**: Following chemotherapy or radiation therapy, typically with a more aggressive course.

Pathophysiology

- Clonal expansion of abnormal hematopoietic stem cells leads to dysplastic (abnormal) maturation in one or more cell lines (erythroid, granulocytic, or megakaryocytic).
- Accumulation of genetic mutations (e.g., TP53, SF3B1) disrupts normal hematopoiesis and promotes ineffective cell production and apoptosis in the bone marrow.

Clinical Features

- **Cytopenia Symptoms**:
  - **Anemia**: Fatigue, pallor, weakness.
  - **Neutropenia**: Increased susceptibility to infections.
  - **Thrombocytopenia**: Easy bruising, bleeding, petechiae.
- **Systemic**: Unexplained fever, weight loss in advanced disease.

Diagnostic Criteria and Classification

Parameter	Details
Bone Marrow Biopsy	Hypercellular marrow with dysplastic changes in ≥10% of cells in one or more lineages.
Peripheral Blood Smear	Shows cytopenias, macrocytic red cells, abnormal neutrophils (e.g., hypogranulation).
Cytogenetic Analysis	Identification of chromosomal abnormalities (e.g., 5q-, 7q-, 20q-deletions).
Molecular Testing	TP53, SF3B1, ASXL1 mutations commonly seen in MDS, can guide prognosis and therapy.
WHO Classification	Based on number of dysplastic lineages, presence of excess blasts, and specific mutations.

Risk Stratification and Prognosis

Risk Factor	Details
Blast Count	Higher percentage of blasts in marrow or peripheral blood indicates a poorer prognosis.
Cytogenetic Abnormalities	Complex karyotypes or specific abnormalities (e.g., TP53 mutation) worsen prognosis.
IPSS-R Scoring System	Assesses five factors (cytopenias, blast %, karyotype) to determine low- to high-risk MDS.

Treatment

1. **Supportive Care**:
   - **Blood Transfusions**: Red cell or platelet transfusions as needed.
   - **Erythropoiesis-Stimulating Agents (ESAs)**: For anemia, especially in lower-risk patients.
2. **Disease-Modifying Therapies**:
   - **Hypomethylating Agents**: Azacitidine, decitabine for intermediate- to high-risk MDS.
   - **Lenalidomide**: Especially effective in MDS with isolated del(5q) mutation.
3. **Allogeneic Stem Cell Transplantation**:
   - Potentially curative for high-risk or younger patients, but carries significant risk and is often reserved for select cases.
4. **Immunosuppressive Therapy**:
   - Considered in specific subtypes (e.g., hypoplastic MDS), may involve antithymocyte globulin (ATG) or cyclosporine.

macrocytic anaemia, thrombocytopenia and neutropenia with a small number of circulating blasts → suggests a diagnosis of myelodysplastic syndrome

Polycythemia

Definition

- Polycythaemia, or erythrocytosis, is a condition characterized by an increased red blood cell mass, leading to elevated hematocrit and hemoglobin levels. It can be **primary** (clonal or intrinsic to bone marrow) or **secondary** (due to external factors stimulating erythropoiesis).

Types and Etiology

Type	Etiology
Primary Polycythaemia	**Polycythaemia Vera (PV)**: A myeloproliferative disorder, most commonly associated with JAK2 mutations.
Secondary Polycythaemia	**Hypoxia-Driven**: High-altitude living, chronic lung disease, obstructive sleep apnea, congenital heart disease. **Erythropoietin (EPO) Secreting Tumors**: Renal cell carcinoma, hepatocellular carcinoma. **Exogenous EPO Use**: Often in athletes or individuals using EPO as a performance-enhancer.
Relative Polycythaemia	Due to decreased plasma volume, as seen in dehydration or stress, rather than increased RBC production.

Pathophysiology

- **Primary Polycythaemia (PV)**: Clonal proliferation in the bone marrow due to a mutation (commonly JAK2 V617F) increases red blood cell production independently of EPO levels.
- **Secondary Polycythaemia**: Increased EPO secretion or hypoxia-driven erythropoiesis stimulates RBC production in response to hypoxia or abnormal EPO production.

Clinical Features

- **Symptoms**: Headache, dizziness, visual disturbances, pruritus (often after hot baths in PV), erythromelalgia (burning pain in hands/feet with redness), and fatigue.
- **Signs**: Facial plethora, splenomegaly (especially in PV), hypertension, and in severe cases, thrombotic events (DVT, stroke).

Diagnostic Evaluation

Test	Findings in Polycythaemia
Complete Blood Count	Elevated hematocrit (>52% in men, >48% in women) and hemoglobin levels.
Erythropoietin (EPO) Level	Low in PV (primary polycythaemia) and elevated in secondary polycythaemia.
JAK2 Mutation Testing	Positive in approximately 95% of PV cases (JAK2 V617F mutation or exon 12 mutation).
Oxygen Saturation	Low in hypoxia-driven polycythaemia (e.g., COPD, sleep apnea).
Imaging	Abdominal ultrasound or CT to assess for splenomegaly or EPO-secreting tumors.

Diagnostic Criteria for Polycythaemia Vera (PV) - WHO 2016

1. **Major Criteria:**
   - Elevated hemoglobin (>16.5 g/dL in men, >16 g/dL in women) or hematocrit.
   - Bone marrow biopsy showing hypercellularity with increased erythroid, granulocytic, and megakaryocytic proliferation.
   - Presence of JAK2 V617F or exon 12 mutation.
2. **Minor Criterion:**
   - Subnormal serum EPO level.

Diagnosis of PV: Requires all 3 major criteria or the first 2 major criteria and the minor criterion.

Management

1. **Phlebotomy**: First-line for PV to maintain hematocrit <45% in men and <42% in women.
2. **Low-Dose Aspirin**: Reduces the risk of thrombosis in PV patients unless contraindicated.
3. **Cytoreductive Therapy**:
   - **Hydroxyurea**: Indicated for high-risk patients (e.g., older age, history of thrombosis).
   - **Ruxolitinib**: JAK2 inhibitor used in PV patients who are resistant or intolerant to hydroxyurea.
4. **Management of Secondary Polycythaemia**: Treat underlying causes (e.g., oxygen therapy for COPD, treatment of EPO-secreting tumors).

Complications

- **Thrombosis**: Risk of arterial and venous thrombotic events is significantly increased in PV.
- **Progression to Myelofibrosis**: Bone marrow fibrosis may develop over time, leading to cytopenias.
- **Transformation to Acute Myeloid Leukemia (AML)**: Rare but more common in patients treated with certain cytotoxic agents.
- **Secondary Polycythaemia**: Prognosis varies based on the underlying cause.

Key Points for MRCP

1. **JAK2 Mutation**: Essential for diagnosing PV; secondary polycythaemia usually has a high EPO level and no JAK2 mutation.
2. **Thrombosis Prevention**: Phlebotomy and low-dose aspirin are mainstays of PV treatment.
3. **Monitor for Transformation**: Regular follow-up to assess for progression to myelofibrosis or AML.

Elevated RBC Count with Normal Haemoglobin and Haematocrit

Definition:

An isolated elevation in red blood cell (RBC) count with normal haemoglobin (Hb) and haematocrit (Hct) suggests an imbalance in red cell indices without corresponding erythrocytosis. This can occur in conditions affecting red cell production, plasma volume, or erythrocyte characteristics.

Causes:

1. Spurious/Physiological Variations:

- **Dehydration (early stages):**
  - Plasma volume contraction may transiently raise RBC count before impacting Hb and Hct.
- **Athletes:**
  - Increased RBC count due to haemodilution from expanded plasma volume ("sports pseudo-anaemia").

2. Microcytosis or Thalassaemia Traits:

- **Thalassaemia Trait (especially β-thalassaemia minor):**
  - Increased RBC count due to compensatory erythropoiesis.
  - Hb and Hct remain normal or slightly reduced.
  - **Key Clue**: Reduced **mean corpuscular volume (MCV)** and **mean corpuscular haemoglobin (MCH).**

3. Iron Deficiency (Early or Subclinical):

- In response to reduced haemoglobin synthesis, the bone marrow may produce more RBCs.
- Hb and Hct may remain normal initially.

4. Chronic Hypoxia (Mild or Intermittent):

- Early compensatory response to hypoxia (e.g., obstructive sleep apnoea, early lung disease).
- May not yet manifest as polycythaemia.

5. Endocrine Disorders:

- **Hyperthyroidism**:
  - Mild increase in RBC production due to increased metabolic demand.
- **Androgen Therapy**:
  - Testosterone stimulates erythropoiesis.

6. Polycythaemia Vera (Early Stage):

- RBC elevation may precede Hb/Hct abnormalities.
- Check for **JAK2 mutations** and EPO levels.

7. Relative Changes in Plasma Volume:

- **Overhydration**:
  - Dilutional effect masks haemoglobin and haematocrit changes.
- **Post-Surgery** or recovery from acute illness:
  - Plasma shifts can transiently elevate RBC count.

8. Laboratory Errors:

- Instrument calibration issues or improper sample handling.

Investigations:

Test	Purpose
Peripheral Blood Film	Evaluate RBC morphology (microcytosis, hypochromia).
MCV, MCH, RDW	Identify microcytosis or iron deficiency.
Serum Ferritin	Assess for iron deficiency.
Haemoglobin Electrophoresis	Rule out thalassaemia traits.
Erythropoietin (EPO)	Low in polycythaemia vera, high in hypoxia-driven causes.
JAK2 Mutation Testing	Diagnose early-stage polycythaemia vera.
Arterial Blood Gas (ABG)	Check for chronic hypoxia.

Management:

1. **Treat Underlying Cause**:
    - Iron supplementation in deficiency.
    - Lifestyle changes for hypoxia (e.g., weight loss, smoking cessation).
    - Manage thalassaemia trait symptomatically.
2. **Monitor Progression**:
    - Repeat FBC if transient causes (e.g., dehydration or stress) are suspected.
3. **Further Evaluation**:
    - Persistent isolated RBC elevation warrants workup for early polycythaemia or chronic hypoxia.

Key Points for MRCP:

1. **Thalassaemia trait** is a common cause of high RBC count with normal Hb and Hct. Look for **microcytosis**.
2. Early **polycythaemia vera** may present with isolated RBC elevation; test for **JAK2 mutations** and EPO levels.
3. Always assess for **chronic hypoxia** and plasma volume changes before concluding the cause.

Thrombocytopenia

Definition

- Low platelet count (<150,000 per microliter).
- Platelet lifespan: Approximately 5 days.

Mechanisms of Thrombocytopenia

1. **Decreased Production**: Bone marrow infiltration, suppression, or fibrosis.
2. **Increased Destruction**: Conditions like DIC, ITP, TTP, and HUS.
3. **Sequestration**: Often due to splenomegaly.
4. **Dilutional**: Secondary to massive transfusions.

Differential Diagnosis

1. **Primary Bone Marrow Disorders**
2. **Chronic Liver Disease**
3. **Infection** (e.g., viral infections like EBV, HIV)
4. **Drug-Related** (e.g., quinine, diuretics, sulfonamides)
5. **Autoimmune/Rheumatological Disorders** (e.g., SLE, antiphospholipid syndrome)
6. **Malignancy**: Occult malignancy or hematological malignancies.
7. **Pseudothrombocytopenia**: Platelet clumping in EDTA tubes; use citrate- or heparin-coated tubes.

Specific Types of Thrombocytopenia

Type	Features	Management
Gestational Thrombocytopenia	Prevalence: 5-10% of pregnancies Mild isolated thrombocytopenia (100,000 - 149,000/microliter)	No intervention needed; monitor counts. Severe cases: steroids and IVIG if platelet <30,000 before delivery.
Immune Thrombocytopenia (ITP)	Often post-viral with marked thrombocytopenia; patient generally well Diagnosis of exclusion	Observation if no major bleeding; may resolve spontaneously.
Drug-Induced	Often linked to medications like aspirin, thiazides, or sulfonamides	Discontinue offending drug.

Investigations

Investigation	Findings/Implications
Peripheral Blood Smear	**Schistocytes**: Suggests TTP, HUS, or DIC **Blasts**: Acute leukemia **Rouleaux**: Multiple myeloma **Atypical Lymphocytes**: Mononucleosis **Macrocytosis**: Alcohol use, B12, or folate deficiency
Serum Creatinine	Elevated in TTP, HUS, sepsis, or multiple myeloma.
Liver Function Tests (LFTs)	**↓Albumin & ↑Bilirubin**: Cirrhosis **↑Transaminases**: Infection (e.g., malaria, EBV) **↑Indirect Bilirubin**: Haemolysis
D-Dimer	Elevated in DIC; normal in TTP.
LDH and Reticulocyte Count	Elevated in haemolysis.
Bone Marrow Biopsy	Considered if cause is unclear; evaluates marrow production issues.
Antibody Testing	Rule out HIT (anti-PF4 antibody test) and autoimmune causes.

Causes of Thrombocytopenia

Severe Thrombocytopenia	Moderate Thrombocytopenia
Immune Thrombocytopenia (ITP)	Heparin-Induced Thrombocytopenia (HIT)
Disseminated Intravascular Coagulation (DIC)	Viral infections (EBV, HIV, hepatitis)
Thrombotic Thrombocytopenic Purpura (TTP)	Alcohol, liver disease
Hematological Malignancies	Hypersplenism, gestational thrombocytopenia
Drug-Induced (e.g., aspirin, sulfonamides)	SLE/antiphospholipid syndrome

Safety Thresholds for Procedures

- **Minor Procedures**: Safe with platelet count of 10-20 ×10^9/L.
- **Major Surgery, CNS, and Eye Procedures**: Platelet count should be above 50 ×10^9/L.

Giant Platelet Syndrome: Bernard-Soulier Syndrome (BSS)

Definition:

- Bernard-Soulier Syndrome (BSS) is a rare autosomal recessive platelet disorder characterized by **giant platelets**, thrombocytopenia, and defective platelet adhesion due to abnormalities in the **GPIb-IX-V complex**, a receptor for von Willebrand factor (vWF).

Pathophysiology:

- The **GPIb-IX-V complex** on platelets mediates the binding of platelets to vWF, a critical step in platelet adhesion at sites of vascular injury.
- Mutations in the **GPIBA**, **GPIBB**, or **GP9** genes disrupt this receptor, leading to defective platelet adhesion.

Clinical Features:

1. **Bleeding Symptoms**:
   - Easy bruising.
   - Prolonged bleeding from minor wounds.
   - Mucosal bleeding (epistaxis, menorrhagia, gastrointestinal bleeding).
   - Severe bleeding after trauma or surgery.
2. **Thrombocytopenia**:
   - Platelet counts typically range from 20–100 × 10^9/L.
3. **Giant Platelets**:
   - Platelets are larger than normal and can be mistaken for red blood cells on blood smears.

Laboratory Findings:

Investigation	Findings
Platelet Count	Mild to moderate thrombocytopenia.
Peripheral Blood Smear	Giant platelets (large, irregular platelets).
Bleeding Time	Prolonged (due to defective adhesion).
Platelet Aggregation Studies	Normal response to ADP, collagen, and thrombin but **no response to ristocetin**.
Flow Cytometry	Reduced or absent expression of the **GPIb-IX-V complex**.
Genetic Testing	Confirms mutations in **GPIBA**, **GPIBB**, or **GP9** genes.

Differential Diagnosis:

- **Von Willebrand Disease (vWD)**:
  - Normal platelet morphology; aggregation improves with addition of vWF.
- **Immune Thrombocytopenia (ITP)**:
  - No giant platelets, platelet destruction due to autoantibodies.
- **Myeloproliferative Disorders**:
  - Giant platelets seen, but usually with elevated WBCs and splenomegaly.

Management:

1. **Preventive Measures**:
   - Avoidance of antiplatelet drugs (e.g., aspirin, NSAIDs).
   - Bleeding risk education.

2. **Treatment for Bleeding Episodes**:
   - Platelet transfusions for severe bleeding.
   - **Desmopressin (DDAVP)** may be considered in some cases to enhance platelet-vWF interaction.
   - **Recombinant Factor VIIa** in refractory cases.
3. **Surgical or Trauma-Related Management**:
   - Prophylactic platelet transfusions before surgery.
4. **Genetic Counseling**:
   - Important for affected families due to autosomal recessive inheritance.

Prognosis:

- Bleeding symptoms are lifelong and vary in severity.
- With proper management, life expectancy is normal.

Key Points for MRCP:

1. **Defective GPIb-IX-V complex** is the hallmark of BSS.
2. **Giant platelets** and thrombocytopenia are distinguishing features on a peripheral smear.
3. **Absent response to ristocetin** is diagnostic.
4. BSS must be differentiated from vWD and other platelet disorders.

Wiskott-Aldrich syndrome (WAS)

Definition

- An X-linked condition characterized by **thrombocytopenia** (micro-thrombocytopenia with small platelets), **eczema**, and **recurrent infections** due to immunodeficiency.

Complications

- **Autoimmunity**: Occurs in 26% to 72% of cases.
- **Increased Risk of Hematological Malignancies**: Especially leukemia and lymphoma.

Diagnosis

Test	Purpose/Findings
WAS Protein (WASp) Analysis	Suggestive of diagnosis if low or absent levels.
WASp Gene Mutation Analysis	Definitive test, detecting mutations in about 99% of affected males.
Immunoglobulin Levels	Often normal IgG, raised IgA, and low IgM in older patients (assessed before treatment initiation).

Treatment

1. **General Management**:
   - **Observation**: If patient is clinically well.
2. **Infection Prophylaxis**:
   - **Prophylactic Antibiotics**: For frequent infections.
     - **Trimethoprim/sulfamethoxazole**:
       - Children >2 months: 2.5 mg/kg orally twice daily.
       - Adults: 160 mg orally twice daily.
     - **Azithromycin** (if TMP/SMX is contraindicated):
       - 10 mg/kg orally once daily for 3 consecutive days every 14 days (max 500 mg/day).

3. **Immunoglobulin Replacement**:
   - For persistent or worsening symptoms, administer **IV or subcutaneous immunoglobulin**.
     - Dosage: 400-600 mg/kg every 3–4 weeks IVIG (or divided doses once/twice weekly subcutaneously).
4. **Thrombocytopenia Treatment**:
   - **Platelet Transfusion**: First-line for significant thrombocytopenia. Use irradiated, cytomegalovirus (CMV) negative blood products.
   - **Steroids** (Prednisolone or Methylprednisolone):
     - Prednisolone: 2 mg/kg/day for 1-2 weeks, then taper (max 60 mg/day).
     - Methylprednisolone: 4 mg/kg/day orally or IV for 1-2 weeks, then taper (max 60 mg/day).
   - **Additional Agents**:
     - **IVIG** and **Rituximab**: Effective for autoimmune cytopenias like hemolytic anemia, thrombocytopenia, or neutropenia.
5. **Specialized Interventions**:
   - **Elective Splenectomy**: Considered for severe thrombocytopenia in the absence of immunodeficiency and autoimmunity.
   - **Bone Marrow Transplantation (BMT)**: The only curative treatment for WAS.

Idiopathic thrombocytopenic purpura (ITP)

Category	Details
Definition	An autoimmune disorder characterized by isolated thrombocytopenia due to autoantibody-mediated platelet destruction.
Epidemiology	Affects both children and adults; often acute in children (post-viral) and chronic in adults.
Pathophysiology	Autoantibodies (typically IgG) target platelet surface glycoproteins, leading to splenic destruction of platelets.
Clinical Features	- **Bleeding Manifestations**: Petechiae, purpura, mucosal bleeding (e.g., gums, epistaxis). - **Absence of Systemic Illness**: Unlike other thrombocytopenias associated with systemic symptoms.
Diagnosis	- **CBC**: Isolated thrombocytopenia; other counts typically normal. - **Peripheral Blood Smear**: Normal morphology except for reduced platelet count. - **Exclusion of Other Causes**: Diagnosis of exclusion.
Differential Diagnosis	Consider conditions like aplastic anemia, leukemias, HIV, hepatitis C, systemic lupus erythematosus (SLE), and drug-induced thrombocytopenia.

Category	Details
Treatment	- **Observation**: For mild cases with platelet count >30,000/µL and no significant bleeding. - **First-Line Therapy**: Corticosteroids (prednisolone 1-2 mg/kg/day), IV immunoglobulin (IVIG), or anti-D immunoglobulin in Rh-positive patients. - **Second-Line Therapy**: Rituximab or splenectomy for refractory cases. - **Thrombopoietin Receptor Agonists** (e.g., romiplostim, eltrombopag) for chronic ITP not responding to first-line treatments.
Monitoring	Regular platelet counts; assess bleeding risk and treatment side effects.
Complications	- **Bleeding Risk**: Particularly with platelet counts <10,000/µL. - **Steroid Side Effects**: In chronic use (e.g., osteoporosis, hypertension).
Prognosis	- **Children**: Typically self-limited, with spontaneous remission in most cases. - **Adults**: Chronic ITP more common, with variable response to treatment.
Key Points for MRCP	- ITP is a diagnosis of exclusion. - First-line treatment includes corticosteroids and IVIG. - Splenectomy can provide long-term remission in refractory cases.

Thrombotic thrombocytopenic purpura (TTP)

Category	Details
Definition	A rare but life-threatening thrombotic microangiopathy characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and widespread platelet aggregation in microcirculation.
Etiology	- **Primary (Idiopathic)**: Often due to autoantibodies against ADAMTS13 enzyme. - **Secondary Causes**: Associated with pregnancy, HIV, certain drugs (e.g., quinine, ticlopidine), malignancy, and autoimmune conditions (e.g., SLE).
Pathophysiology	- Deficiency of ADAMTS13 (a metalloprotease that cleaves von Willebrand factor) leads to accumulation of large vWF multimers, causing platelet aggregation and microvascular thrombosis. - Results in thrombocytopenia and mechanical hemolysis of red blood cells.
Clinical Features	**Pentad** of symptoms: - **Thrombocytopenia**: Causes petechiae, purpura, and mucosal bleeding. - **Microangiopathic Hemolytic Anemia (MAHA)**: Fatigue, jaundice, schistocytes on blood smear. - **Neurological Symptoms**: Headache, confusion, seizures, or coma. - **Renal Dysfunction**: Proteinuria, hematuria, mild renal impairment. - **Fever**: Low-grade and often variable.

Category	Details
Diagnosis	- **CBC and Peripheral Blood Smear**: Thrombocytopenia and presence of schistocytes (fragmented red cells). - **Lactate Dehydrogenase (LDH)**: Elevated due to hemolysis. - **Indirect Bilirubin**: Elevated in hemolysis. - **Haptoglobin**: Decreased. - **ADAMTS13 Activity**: Severely reduced (<10%) in primary TTP; detection of anti-ADAMTS13 antibodies in idiopathic cases.
Differential Diagnosis	Consider hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), and severe hypertension-associated thrombotic microangiopathy.
Treatment	- **Plasma Exchange (Plasmapheresis)**: First-line and life-saving; daily exchanges until remission (i.e., normalization of platelet count and LDH). - **Corticosteroids**: Often added to reduce autoimmune response. - **Rituximab**: Considered for refractory or relapsed TTP. - **Caplacizumab**: Anti-vWF therapy used in severe cases for faster platelet count normalization. - **Supportive Care**: Avoid platelet transfusions unless life-threatening hemorrhage occurs.
Complications	- **Renal Failure**: May require dialysis in severe cases. - **Neurological Sequelae**: Possible long-term cognitive and neurological deficits. - **Relapse**: Risk of relapse in up to 30-50% of cases, particularly in those with persistent ADAMTS13 deficiency.
Prognosis	With timely plasma exchange, prognosis has significantly improved; however, relapse is common, requiring regular follow-up and monitoring for ADAMTS13 levels.
Key Points for MRCP	- Classic pentad includes thrombocytopenia, MAHA, neurological symptoms, renal impairment, and fever. - Immediate plasma exchange is critical to improve survival. - Avoid platelet transfusions, as it may worsen microvascular thrombosis.

Investigations

Initial tests

- **CBC (↓ Platelets, ↓ Hemoglobin)**
- **Peripheral blood smear (↑ schistocytes ↓ platelets)**
- **Hemolysis studies (↑ Reticulocytes, ↓ Haptoglobin, ↑ LDH, ↑ indirect bilirubin)**
- **RFT (↑ Urea, creatinine)**

Confirmatory test

- **ADAMTS13 activity (test before starting plasma exchange or pRBC; do not delay treatment waiting for results)**

Management

- **Plasma exchange therapy (PEX) to remove antibodies → the treatment of choice**
- **Immunosuppression (after PEX) → High-dose glucocorticoids and Rituximab (anti- CD20)**
- **Caplacizumab → binds to von Willebrand factor, inhibiting it from interacting with platelets and preventing clots**

TTP vs HUS

Comparison between Thrombotic thrombocytopenic purpura (TTP) and Haemolytic-uremic syndrome (HUS).

TTP vs HUS	Thrombotic thrombocytopenic purpura (TTP)	Haemolytic-uremic syndrome (HUS)
patient groups	Common in **adults**	Common in **children** (90%)
history of diarrhoeal illness	Less common	More common
Acute kidney injury	Less sever	**More sever**
Neurological symptoms	**More common**	**Less common**
ADAMTS13 activity	**Low**	Normal
Plasma exchange (PEX)	greatly reduces the mortality	controversial

Differentiation between Thrombotic thrombocytopenic purpura (TTP), Disseminated intravascular coagulation (DIC) and Immune thrombocytopenia (ITP).

	Thrombotic thrombocytopenic purpura (TTP)	Disseminated intravascular coagulation (DIC)	Immune thrombocytopenia (ITP)
Pathogenesis	Endothelial defect	Thrombin excess	Anti-platelet antibodies
Clinical condition	Sick	Sick	Not sick
Red cells	Schistocytes	Schistocytes +/-	NIL
PT (INR)	NIL/ Slight increase	Increase	NIL
PTT	NIL/ Slight increase	Increase	NIL
Fibrinogen	NIL	Decrease	NIL
Fibrin monomers	Slight increase	Increase	NIL
Fibrin degradation	Slight increase	Increase	NIL
D-dimers	Slight increase	Increase	NIL
Therapy	Plasma exchange Vincristine	Rx cause Plasma/Platelets	Steroids IVIG Splenectomy

Haemolytic uraemic syndrome (HUS)

Category	Details
Definition	A thrombotic microangiopathy primarily affecting children, characterized by the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury (AKI).
Etiology	- **Typical HUS (Shiga Toxin-Associated)**: Often follows gastrointestinal infection with Shiga toxin-producing *Escherichia coli* (STEC), commonly serotype O157 . - **Atypical HUS**: Not associated with infection; often due to genetic mutations affecting the complement pathway or triggered by other factors like pregnancy, medications, or autoimmune diseases.
Pathophysiology	- Shiga toxin damages endothelial cells, leading to platelet aggregation, microthrombi formation, and mechanical hemolysis. - In atypical HUS, dysregulation of the complement system causes similar endothelial damage and thrombosis in small vessels, particularly in the kidneys.
Clinical Features	**Triad of Symptoms**: - **Microangiopathic Hemolytic Anemia (MAHA)**: Fatigue, pallor, jaundice, presence of schistocytes on blood smear. - **Thrombocytopenia**: Petechiae, purpura, and mucosal bleeding. - **Acute Kidney Injury**: Oliguria, hematuria, proteinuria, elevated creatinine. **Other Symptoms**: Abdominal pain, diarrhea (often bloody) in STEC-HUS, hypertension, edema, and neurological symptoms in severe cases.

Category	Details
Diagnosis	- **CBC and Peripheral Blood Smear**: Thrombocytopenia and schistocytes (fragmented RBCs). - **Lactate Dehydrogenase (LDH)**: Elevated due to hemolysis. - **Indirect Bilirubin**: Elevated due to hemolysis. - **Haptoglobin**: Decreased. - **Renal Function Tests**: Elevated creatinine and blood urea nitrogen (BUN). - **Stool Culture**: Positive for Shiga toxin-producing *E. coli* in typical HUS. - **Complement Testing**: Low levels (C3 and C4) in atypical HUS; genetic testing for complement mutations in familial cases.
Differential Diagnosis	Consider thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), systemic lupus erythematosus (SLE), and vasculitis.
Treatment	- **Supportive Care**: Mainstay for typical HUS, including fluid management, blood pressure control, and correction of electrolyte abnormalities. - **Dialysis**: Often needed in cases of severe kidney failure. - **Plasma Exchange**: Considered in atypical HUS or severe cases unresponsive to supportive care. - **Eculizumab**: Monoclonal antibody against complement protein C5, used in atypical HUS to prevent complement-mediated damage. - **Avoid Antibiotics and Antimotility Agents**: Especially in STEC-HUS, as they may worsen toxin release and kidney injury.
Complications	- **Chronic Kidney Disease (CKD)**: Long-term renal impairment in up to 50% of severe cases. - **Hypertension**: Persistent hypertension may develop due to renal damage. - **Neurological Sequelae**: Possible in severe cases with central nervous system involvement.
Prognosis	- **Typical HUS**: Generally favorable with supportive care, although long-term renal issues can persist. - **Atypical HUS**: Higher morbidity and relapse rates, often requiring ongoing complement-inhibitor therapy.
Key Points for MRCP	- Classic triad includes MAHA, thrombocytopenia, and AKI. - Avoid antibiotics in STEC-HUS. - Eculizumab is effective in atypical HUS associated with complement dysregulation.

Disseminated intravascular coagulation (DIC)

Category	Details
Definition	A systemic process leading to widespread activation of the coagulation cascade, resulting in both thrombosis and bleeding due to consumption of clotting factors and platelets.
Etiology	- **Infections**: Commonly seen in sepsis, particularly from gram-negative bacteria. - **Obstetric Complications**: Amniotic fluid embolism, placental abruption. - **Malignancy**: Solid tumors (e.g., pancreatic, gastric cancer), acute promyelocytic leukemia (APL). - **Trauma and Surgery**: Major trauma, severe burns, liver disease. - **Other**: Snake bites, heat stroke, shock.
Pathophysiology	- Triggering event (e.g., infection, trauma) leads to widespread endothelial damage and release of procoagulants, activating the coagulation cascade. - Formation of microthrombi leads to organ ischemia, while consumption of platelets and clotting factors causes bleeding.
Clinical Features	**Thrombotic and Hemorrhagic Manifestations**: - **Bleeding**: Mucosal bleeding, petechiae, purpura, ecchymoses, and oozing from venipuncture sites. - **Thrombosis**: Microvascular thrombosis leading to organ dysfunction (e.g., renal failure, liver dysfunction, respiratory distress). - **Organ Failure**: Respiratory distress, acute kidney injury, altered mental status in severe cases.
Diagnosis	- **CBC**: Thrombocytopenia due to platelet consumption. - **Peripheral Blood Smear**: Schistocytes (fragmented red cells) may be present. - **Coagulation Profile**: - **Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT)**: Prolonged. - **Fibrinogen**: Low, as it is consumed. - **D-Dimer**: Elevated due to fibrinolysis. - **Fibrin Degradation Products (FDPs)**: Elevated, reflecting fibrin breakdown.
Differential Diagnosis	Consider thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and severe liver disease.
Treatment	- **Address Underlying Cause**: Essential to halt the DIC process (e.g., antibiotics for sepsis, delivery in obstetric causes). - **Supportive Management**: - **Platelet Transfusion**: For platelet counts <20,000/μL if bleeding or <50,000/μL for major bleeding or invasive procedures. - **Fresh Frozen Plasma (FFP)**: Replaces clotting factors if bleeding. - **Cryoprecipitate**: For fibrinogen replacement if fibrinogen levels are <100 mg/dL. - **Heparin**: Low-dose heparin in cases with predominant thrombosis and low bleeding risk (rarely used in acute bleeding cases).

Category	Details
Complications	- **Multiorgan Failure**: Due to microvascular thrombosis and ischemia (renal, hepatic, and pulmonary involvement common). - **Hemorrhagic Shock**: Due to severe bleeding. - **Death**: High mortality rate if not promptly treated.
Prognosis	Depends on the underlying cause and timely treatment; mortality remains high in severe cases of DIC, especially if associated with sepsis or malignancy.
Key Points for MRCP	- DIC involves both bleeding and thrombosis due to consumption of platelets and coagulation factors. - Treat the underlying cause as the priority. - Elevated D-dimer and low fibrinogen are characteristic findings. - Transfusion support (platelets, FFP, cryoprecipitate) is based on bleeding severity.

the combination of the D-dimer and the FDP assay provides the most rapid and specific diagnosis of DIC.

Thrombocytosis

Aspect	Primary Thrombocytosis (Essential Thrombocythemia - ET)	Secondary (Reactive) Thrombocytosis
Definition	Myeloproliferative disorder with autonomous overproduction of platelets	Elevated platelet count in response to another condition (e.g., inflammation)
Causes	Mutations in JAK2, CALR, MPL genes	Infection, inflammation, iron deficiency, splenectomy, malignancy
Clinical Features	- Often asymptomatic - Burning pain in hands/feet (erythromelalgia) - Headache, dizziness, visual disturbances - Risk of thrombosis or bleeding	- Usually asymptomatic - Symptoms related to the underlying cause
Investigations	- **CBC**: Platelets >450,000/µL - **Bone Marrow Biopsy**: Increased megakaryocytes and cellularity - **Genetic Testing**: JAK2, CALR, MPL mutations	- **CBC**: Platelets >450,000/µL - Tests for underlying cause: CRP, ESR, ferritin, iron studies
Management	- **Low-Risk**: Observation, low-dose aspirin - **High-Risk**: Hydroxyurea, interferon-α, aspirin - **Plateletpheresis** in emergencies	- Treat underlying cause (e.g., antibiotics for infection) - Platelet count normalizes when cause is resolved
Complications	Thrombosis, bleeding in extreme cases	Rare, usually resolves with treatment of the underlying condition
Prognosis	Good with management, risk of transformation to myelofibrosis or acute leukemia	Generally favorable; resolves with treatment of underlying condition

Essential thrombocytosis (ET)

Definition

- Essential thrombocytosis is a myeloproliferative disorder characterized by excessive platelet production due to megakaryocyte proliferation without an identifiable cause. It overlaps with other myeloproliferative disorders like chronic myeloid leukemia, polycythemia vera, and myelofibrosis.

Epidemiology

- Commonly affects adults aged 50–70 years.
- Occurs equally in males and females.

Clinical Features

- Often asymptomatic (25-33%).
- Symptoms may include tingling or burning in hands and feet, erythromelalgia (burning pain, warmth, redness of extremities), headache, visual issues, weakness, dizziness, sweating, low-grade fever, and pruritus.
- Splenomegaly (40-50%) and hepatomegaly (20%) may be present.
- Both thrombosis and hemorrhage are possible.

Diagnostic Criteria

1. **Sustained Platelet Count**: ≥450 × 10^9/L.
2. **Genetic Mutation**: Presence of acquired mutations (JAK2, CALR, or MPL).
3. **Exclusion of Other Myeloid Malignancies**: Rule out polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome.
4. **No Reactive Cause**: Rule out secondary causes, with normal iron levels.
5. **Bone Marrow Findings**: Increased megakaryocytes with hyperlobated nuclei and abundant cytoplasm; mild reticulin fibrosis (grades 0–2/4).

Diagnosis requires criteria 1–3 or 1 + 3–5.

Adverse Prognostic Markers

- Age >60
- Thrombosis history or platelet count >1500
- Obesity and cardiovascular risk factors (smoking, hypertension, hypercholesterolemia)
- Markers of hypercoagulability (e.g., Factor V Leiden, antiphospholipid antibodies)
- JAK2 mutation

Investigations

- **CBC**: Platelet count >600 × 10^9/L; possible mild elevation in RBC or WBC.
- **Genetic Testing**: JAK2 mutation (50-60%), CALR (25%), MPL (3-5%).
- **Bone Marrow Biopsy**: Increased cellularity with megakaryocytic hyperplasia.
- **Vitamin B12** and **uric acid** levels may be elevated.
- **C-reactive protein (CRP)**, **fibrinogen**, and **interleukin-6** to exclude secondary thrombocytosis.

Management

- **Low-Risk Patients**: Observation only.
- **High-Risk Patients** (age >60, history of thrombosis, or platelets >1500):
  - **Hydroxyurea (hydroxycarbamide)**: First-line to reduce platelet count.
  - **Interferon-α**: Preferred for younger patients and during pregnancy.
  - **Low-Dose Aspirin**: Reduces thrombotic risk, especially in patients with JAK2 mutation or microvascular symptoms (e.g., erythromelalgia). Avoid aspirin if ristocetin cofactor level (VWF function) is <30%.
- **Plateletpheresis**: Reserved for cases with extreme thrombocytosis and symptomatic clotting or bleeding.

Prognosis

- Excellent survival expectancy (over two decades).
- Low risk (<1%) of transformation to acute myeloid leukemia.

Von Willebrand's disease

Definition

- Von Willebrand's disease is the most common inherited bleeding disorder, resulting from a deficiency or dysfunction of von Willebrand factor (VWF), which is essential for platelet adhesion and Factor VIII stability.

Basics of VWF

- **Structure**: VWF is a large multimeric glycoprotein.
- **Synthesis and Storage**: Produced in endothelial cells and megakaryocytes, stored in Weibel-Palade bodies and platelet alpha granules.
- **Blood Group Influence**: Adults with blood type O have VWF levels approximately 25-30% lower than other blood types.

Function

- **Platelet Adhesion**: VWF binds to damaged endothelium and promotes platelet adhesion by binding to collagen and Gplb platelet receptor.
- **Carrier for Factor VIII**: Stabilizes Factor VIII and protects it from degradation, contributing to the intrinsic coagulation pathway.

Types of VWD

Type	Inheritance	Mechanism	Prevalence	Severity
Type 1	Autosomal dominant	Partial reduction in VWF	Most common (80%)	Mild
Type 2	Autosomal dominant	Dysfunctional VWF	Less common	Moderate
Type 3	Autosomal recessive	Complete absence of VWF	Rare	Most severe

Clinical Features

- **Bleeding Tendency**: Mimics platelet disorders, causing symptoms like epistaxis and menorrhagia. Hemarthroses and muscle hematomas are rare.
- **Medication Sensitivity**: Symptoms are worsened by drugs that inhibit platelet function, such as aspirin and NSAIDs.

Diagnosis

- **Bleeding Time**: Prolonged due to impaired platelet adhesion.
- **APTT**: May be prolonged due to reduced Factor VIII.
- **Factor VIII Activity**: Often reduced; important for assessing bleeding risk.
- **VWF Antigen and Activity (Ristocetin Cofactor Assay)**: Primary diagnostic test.
- **PT and Platelet Count**: Normal in Type 1 VWD.

Management

- **Major Bleeding or Surgery**:
  - **1st Line**: VWF concentrate (plasma-derived or recombinant).
  - **2nd Line**: Factor VIII (Humate-P, an intermediate-purity Factor VIII concentrate rich in VWF).

- **Minor Bleeding or Minor Surgery**:
  - **1st Line**: DDAVP (desmopressin), which increases VWF release from endothelial cells.
  - **2nd Line**: VWF concentrates if needed.
- **Mild Mucosal Bleeding (e.g., Epistaxis)**: Antifibrinolytic agents like tranexamic acid can be used alone or with DDAVP.
- **Oral Contraceptives**: Can raise VWF levels in women with Type 1 VWD and menorrhagia.

Haemophilia

Definition

Haemophilia is a genetic disorder characterized by a deficiency of clotting factors, primarily affecting:

- **Haemophilia A**: Deficiency in Factor VIII (~80% of cases).
- **Haemophilia B (Christmas Disease)**: Deficiency in Factor IX (~20% of cases).

Epidemiology

- Haemophilia A is more common than Haemophilia B.

Genetics

- **Inheritance**: X-linked recessive, mostly affecting males.
- **Carrier Mothers**: 50% chance of passing the disease to sons and 50% chance of passing the carrier status to daughters.
- **Family History**: Approximately 30% of cases occur without a family history due to new mutations.

Clinical Features by Severity

Severity	Clinical Signs	Factor VIII/IX Activity
Physiologic (Normal)	None	≥ 50%
Mild	Hematomas after severe trauma	>5% to <50%
Moderate	Hematomas after mild trauma	≥1% to 5%
Severe	Spontaneous hematomas	<1%

Note: Petechiae are typical of platelet disorders, not hemophilia.

Diagnosis

- **Coagulation Profile**: Prolonged aPTT; normal bleeding time, thrombin time, and prothrombin time.
- **Mixing Study**: Used if aPTT is prolonged; correction indicates a factor deficiency.
- **Factor Assay**: Plasma Factor VIII and IX levels to confirm specific deficiency.

Treatment

- **Replacement Therapy**: Factor VIII (for Haemophilia A) or Factor IX (for Haemophilia B) replacement.
  - **Side Effect**: Development of antibodies against Factor VIII in about 10–15% of patients.

Heparin

Types and Administration

- **Unfractionated Heparin (UFH):** Given intravenously; short-acting and rapid onset. Activates antithrombin III, forming a complex that inhibits thrombin and factors Xa, IXa, XIa, and XIIa.
- **Low Molecular Weight Heparin (LMWH):** Given subcutaneously; longer-acting with a more predictable effect. Primarily increases antithrombin III activity on Factor Xa.

Key Differences Between UFH and LMWH

Aspect	Unfractionated Heparin (UFH)	Low Molecular Weight Heparin (LMWH)
Administration	Intravenous	Subcutaneous
Duration of Action	Short	Long
Mechanism	Activates antithrombin III, inhibits multiple clotting factors (IIa, Xa, IXa, XIa, XIIa)	Activates antithrombin III, primarily inhibits Factor Xa
Monitoring	Requires APTT	Anti-Factor Xa monitoring (routine monitoring not needed)
Side Effects	Higher risk of HIT and osteoporosis	Lower risk of HIT and osteoporosis
Use	Suitable in high bleeding risk situations due to rapid reversibility	Standard for VTE treatment/prophylaxis, acute coronary syndromes

Heparin-Induced Thrombocytopenia (HIT)

- **Type 1 HIT**: Non-immune, mild thrombocytopenia (platelet count >100,000/mm³) within 1–4 days of heparin. Self-limiting.
- **Type 2 HIT**: Immune-mediated, caused by IgG antibodies against the heparin-PF4 complex. Occurs 5–14 days after starting heparin, with platelet count often <100,000/mm³. High risk of thrombosis despite low platelets.

Features of HIT

- Platelet count falls >50% from baseline.
- Thrombosis risk (both arterial and venous).
- Raised D-dimer due to widespread thrombosis.
- Skin reactions or necrosis may occur.

HIT Diagnosis: 4Ts Scoring System

- **Thrombocytopenia**: Platelet count fall and nadir levels.
- **Timing**: Occurs 5–10 days post-heparin exposure.
- **Thrombosis**: New thrombosis or skin reactions.
- **Thrombocytopenia of Other Causes**: Exclude other causes.

HIT Treatment

1. **Stop Heparin**: Immediately discontinue heparin.
2. **Start Non-Heparin Anticoagulant**: Options include direct thrombin inhibitors (e.g., Lepirudin, Argatroban) or Factor Xa inhibitors (e.g., Fondaparinux, Rivaroxaban).
3. **Avoid Warfarin Initially**: Warfarin can worsen thrombosis if started before platelet recovery; administer after platelet count >150,000/mm³.
4. **Antidote for Heparin**:
   - **UFH**: Reversal with protamine sulfate (1 mg per 100 units of heparin).
   - **LMWH**: Andexanet alfa (preferred) or protamine sulfate if Andexanet alfa is unavailable.

Special Considerations

- **Heparin Resistance**: Can occur due to antithrombin III deficiency, requiring alternative dosing or therapy.
- **Hyperkalemia**: Heparin may induce hyperkalemia in some patients.
- **Heparin Overdose**: Reversible with protamine sulfate for UFH and partially reversible for LMWH with Andexanet alfa or protamine sulfate (as a second-line option).

Fondaparinux

Action	Indirect inhibitor of activated Factor Xa
Prophylactic Dose (Immobility)	2.5 mg once daily, start 6 hours after surgery
Therapeutic Dose (DVT & PE)	With warfarin: 5 mg (up to 50 kg), 7.5 mg (50-100 kg), 10 mg (≥101 kg) once daily; continue until INR ≥2 for 24 hours
Treatment for Superficial-Vein Thrombosis	2.5 mg once daily for at least 30 days
Special Considerations	Avoid if eGFR <30 mL/min/1.73 m²; stop 24 hours before surgery and restart at least 6 hours post-op
Antidote	No specific antidote

Direct Oral Anticoagulants (DOACs)

Drug	Action	Excretion
Apixaban	Direct Factor Xa inhibitor	Majority fecal
Rivaroxaban	Direct Factor Xa inhibitor	Majority hepatic
Dabigatran	Direct thrombin inhibitor	Majority renal

Indications

- Prevention and treatment of DVT and PE
- Prevention of stroke in non-valvular AF
- No routine anticoagulant monitoring required (INR tests are unreliable).

Contra-indications & cautions

- Risk factors for major bleeding
- Antiphospholipid syndrome (increased risk of recurrent thrombotic events) .
- **DOACs are not recommended in patients with antiphospholipid syndrome →** increased risk of thrombotic events compared with warfarin
- **DOACs** efficacy is not established in prosthetic heart valve & valvular AF
- **Avoid in pregnancy and breast feeding.**

Apixaban

Action	Direct inhibitor of activated Factor Xa
Prophylactic Dose (Immobility)	2.5 mg twice daily, start 12–24 hours after surgery
Prophylaxis Dose (Non-Valvular Atrial Fibrillation)	5 mg twice daily; reduce to 2.5 mg twice daily if age ≥80 years, weight <61 kg, or serum creatinine ≥133 µmol/L
Therapeutic Dose (DVT & PE)	Initial: 10 mg twice daily for 7 days, then maintenance 5 mg twice daily for 6 months
Special Considerations	Avoid if creatinine clearance <15 mL/min; reduce to 2.5 mg twice daily if creatinine clearance 15–29 mL/min
Antidote	Andexanet alfa (Ondexxya®)

Rivaroxaban

Action	Direct inhibitor of activated Factor Xa
Prophylactic Dose (Immobility)	10 mg once daily, start 6–10 hours after surgery
Prophylaxis Dose (Non-Valvular Atrial Fibrillation)	20 mg once daily
Therapeutic Dose (DVT & PE)	Initial: 15 mg twice daily for 21 days, then maintenance 20 mg once daily
Special Considerations	Avoid if creatinine clearance <15 mL/min; contraindicated in hepatic disease with coagulopathy; take with food
Antidote	Andexanet alfa (Ondexxya®)

Andexanet Alfa: Factor Xa Inhibitor Reversal Agent

Dose of Factor Xa Inhibitor	Reversal Protocol
Low Dose (Apixaban ≤5 mg or Rivaroxaban ≤10 mg, or last dose ≥8 hours)	400 mg IV bolus (30 mg/min), followed by 4 mg/min IV infusion for up to 120 minutes.
High Dose (Apixaban >5 mg or Rivaroxaban >10 mg, given <8 hours)	800 mg IV bolus (30 mg/min), followed by 8 mg/min IV infusion for up to 120 minutes.

Dabigatran

Feature	Details
Mode of Action	Direct thrombin inhibitor (only oral direct thrombin inhibitor available).
Administration	Given as a prodrug (dabigatran etexilate) and converted to active dabigatran by tissue esterases.
Onset of Action	Rapid onset; anticoagulant effect begins within minutes and peaks after 2–3 hours.
Excretion	Primarily renal (80% excreted via kidneys).
Advantages	- Short half-life, allowing for quicker normalization of coagulation compared to warfarin. - No routine monitoring needed.
Disadvantages	- Not recommended for patients with prosthetic heart valves due to unestablished safety and efficacy. - Higher rates of major bleeding observed compared to warfarin.
Anticoagulant Monitoring	- Routine monitoring usually unnecessary. - Thrombin time (TT), aPTT, and ecarin clotting time can assess anticoagulant effect. - INR and PT are unreliable for dabigatran.
Procedural Bleeding Risk	- Stop dabigatran 1–2 days before surgery if CrCl ≥50 mL/min, or 3–5 days before if CrCl <50 mL/min. - For urgent surgery, assess bleeding risk using aPTT (normal aPTT may suggest lower bleeding risk).
Conversion from Warfarin	Stop warfarin and monitor INR daily; initiate dabigatran once INR <2.0.
Antidote	Idarucizumab: 5 g IV, administered as two separate 2.5 g doses within 15 minutes.
Contraindications	Contraindicated if eGFR <30 mL/min.
Notes	- Ecarin clotting time is specifically prolonged by dabigatran (and other direct thrombin inhibitors). - Idarucizumab is the specific reversal agent for dabigatran.

Warfarin

Warfarin action → inhibition of epoxide reductase → vitamin K inhibition → inhibits clotting factor II, VII, IX and X (mnemonic = 1972) **and protein C.**

Indications

- Venous thromboembolism: (target INR = 2.5, if recurrent 3.5)
- Atrial fibrillation, (target INR = 2.5)
- Mechanical heart valves, (target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves).

Side-effects

- Haemorrhage
- Teratogenic, although can be used in breast-feeding mothers. **the most common teratogenic effect is Nasal hypoplasia**
- Skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- Purple toes

Contraindications: **Pregnancy.**

Monitoring

- International normalised ration (INR), the ratio of the prothrombin time for the patient over the normal prothrombin time.
- Warfarin has a long half-life (44 h) and achieving a stable INR may take several days.

Factors that may potentiate warfarin (increase INR)

- Liver disease
- **P450 enzyme inhibitors**, e.g.: amiodarone, clarithromycin, ciprofloxacin
- Cranberry juice
- NSAIDs (displace warfarin from plasma albumin and inhibit platelet function)

Management of high INR

Situation	Management
Major bleeding	▪ Stop warfarin ▪ Give intravenous vitamin K 5mg ▪ Prothrombin complex concentrate - if not available then FFP
INR > 8.0 Minor bleeding	▪ Stop warfarin ▪ Give intravenous vitamin K 1-3mg ▪ Repeat dose of vitamin K if INR still too high after 24 hours ▪ Restart warfarin when INR < 5.0
INR > 8.0 No bleeding	▪ Stop warfarin ▪ Give vitamin K 1-5mg by mouth, using the intravenous preparation orally ▪ Repeat dose of vitamin K if INR still too high after 24 hours ▪ Restart when INR < 5.0
INR 5.0-8.0 Minor bleeding	▪ Stop warfarin ▪ Give intravenous vitamin K 1-3mg ▪ Restart when INR < 5.0
INR 5.0-8.0 No bleeding	▪ Withhold 1 or 2 doses of warfarin ▪ Reduce subsequent maintenance dose

Prothrombin concentrates are products of choice for warfarin reversal in the setting of active bleeding and a markedly raised INR.

Porphyrias

Definition

- Porphyrias are a group of rare metabolic disorders resulting from enzyme deficiencies in the heme biosynthesis pathway, leading to the accumulation of porphyrins or their precursors, which can cause neurovisceral symptoms, skin lesions, or both.

Acute Intermittent Porphyria (AIP)

Feature	Description
Pathophysiology	Autosomal dominant deficiency of porphobilinogen deaminase, an enzyme in the heme biosynthesis pathway.
Epidemiology	Most common acute porphyria; more common in females (5:1), ages 20-40. Rarely occurs before puberty.
Features	- Abdominal pain, vomiting, constipation. - Neuropsychiatric symptoms (seizures, delirium). - Hypertension, tachycardia, hyponatremia. - Urine turns deep red on standing.
Investigations	- **First-Line**: Urine porphobilinogen (PBG) and total porphyrins. - **Second-Line**: Fecal and plasma porphyrins. - **Confirmation**: Erythrocyte porphobilinogen deaminase activity.
Precipitating Factors	Stress, infection, pregnancy, fasting, drugs (e.g., barbiturates, alcohol, OCPs).
Treatment	- **IV Hemin (Heme Arginate)**: Decreases ALA synthase activity; 3-4 mg/kg IV daily for 4+ days. - **Glucose Loading**: High glucose intake for mild cases. - **Supportive Care**: Analgesics for pain.

Variegate Porphyria (VP)

Pathophysiology	Autosomal dominant defect in protoporphyrinogen oxidase.
Features	Photosensitive blistering rash, abdominal pain, neuropsychiatric symptoms.
Epidemiology	Common in South Africa due to genetic founder effect.
Investigations	Plasma porphyrins show characteristic fluorescence peak at neutral pH; elevated urinary and fecal porphyrins during acute attacks.
Management	Similar to AIP; includes hemin therapy and avoidance of precipitating factors.

Porphyria Cutanea Tarda (PCT)

Feature	Description
Pathophysiology	Deficiency of uroporphyrinogen decarboxylase (UROD), leading to photosensitive porphyria.
Causes	- Inherited or acquired (e.g., alcohol, estrogens, hepatitis C, iron overload from hemochromatosis).
Features	- Photosensitive rash with bullae on sun-exposed areas. - Skin fragility, especially on hands and face. - Scarring following blister healing.
Investigations	- **Initial Test**: Plasma total porphyrins. - Elevated urinary uroporphyrinogen, pink fluorescence under Wood's lamp. - Normal PBG.
Management	- **Avoidance**: Withdraw precipitating factors. - **Phlebotomy**: Weekly venesection until hemoglobin ~120 g/L to reduce iron. - **Chloroquine**: Low-dose may promote porphyrin excretion.

Distinguishing Features of Acute Porphyrias vs. Lead Poisoning

Feature	Acute Porphyria	Lead Poisoning
Anemia	Typically absent in acute porphyrias.	Common, due to enzyme inhibition (e.g., ferrochelatase) and decreased red cell lifespan.
Blood Film	No basophilic stippling.	Basophilic stippling due to accumulation of pyrimidine nucleotides.
Porphyrinuria	Present with elevated PBG and total porphyrins during attacks.	Also present, but usually accompanied by other signs of lead toxicity.

Acute intermittent porphyria: 6 P's

- **Porphobilinogen deaminase deficiency**
- **Pain in abdomen** (most common, 95% of patients experience)
- **Psychological symptoms** (Anxiety, agitation, hallucination, hysteria, delirium, depression)
- **Peripheral neuropathy** (Patchy numbness and paresthesias)
- **Pee abnormality** (Dysuria, urinary retention/incontinence or dark urine)
- **Precipitated by drugs** (e.g. barbiturates, oral contraceptives, Sulfa drugs)

Factors precipitate acute attack (AIP)

- **Stress**
- **Infection**
- **Pregnancy**
- **Menstruation**
- **starvation**, reduced caloric or carbohydrate intake (especially fasting)
- Smoking
- Progesterone
- Drugs

Drugs which may precipitate attack		Safe Drugs
• Alcohol • Phenytoin • Barbiturates • Phenobarbital • Carbamazepine • Topiramate • Valproic acid • Clonazepam (high doses) • Tricyclic antidepressants • Halothane • Oral contraceptive pill • Sulphonamides • Cephalosporins • Erythromycin • Isoniazid • **flucloxacillin** • Anabolic steroids	• Sulphonylureas • Theophylline • Antihistamines • MAOIs • Amiodarone • Simvastatin • **Diuretics** • **Hydralazine** • **Calcium channel blockers** • **ACE inhibitors** • **Rifampin** • **Spironolactone** • **Sulfasalazine** • **Diclofenac** • **Nitrofurantoin**	• Paracetamol • Aspirin • Ibuprofen • Codeine • Morphine • Chlorpromazine • **β-blockers** • **Gabapentin** • Levetiracetam • Penicillin • Aminoglycosides • Doxycycline • Metformin • **Amoxicillin** • **Dapagliflozin, Empagliflozin** • **Benzodiazepines (eg, lorazepam, midazolam)**

Note: Levetiracetam and gabapentin are among the few anti-epileptics considered safe.

Hodgkin's lymphoma (HL)

Definition:

- Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterized by the presence of Reed-Sternberg cells, originating from mature B cells.

Epidemiology

- **Age Distribution**: Bimodal peak incidence, most common in the third and seventh decades.

Risk Factors

- Epstein-Barr virus (EBV) infection
- Family history of HL
- Immunodeficiency (e.g., HIV, organ transplant)
- Autoimmune diseases (e.g., rheumatoid arthritis, sarcoidosis)

Clinical Features

- **Lymphadenopathy**: Painless, often in cervical nodes (~60–70% of patients).
- **Mediastinal Mass**: May cause chest pain, cough, and dyspnea.
- **B Symptoms**: Night sweats, unexplained weight loss (>10% in 6 months), fever >38°C.
- **Pel-Ebstein Fever**: Intermittent fever with febrile and afebrile periods.
- **Other Symptoms**: Alcohol-induced pain, pruritus, hepatosplenomegaly.

Histological Classification

Type	Frequency	Prognosis	Notes
Nodular Sclerosing	~70%	Good prognosis	Common in women, associated with lacunar cells.
Mixed Cellularity	~20%	Good prognosis	High Reed-Sternberg cell count.
Lymphocyte Predominant	~5%	Best prognosis	Rare and favorable.
Lymphocyte Depleted	Rare	Worst prognosis	Least common, poor outcome.

Staging: Ann-Arbor Classification

Stage	Description
I	Involvement of a single lymph node region.
II	Involvement of two or more lymph node regions on the same side of the diaphragm.
III	Involvement of lymph nodes on both sides of the diaphragm (e.g., includes spleen).
IV	Diffuse or disseminated involvement of one or more extralymphatic organs.

- **Subclassification**:
  - **A**: No B symptoms.
  - **B**: Presence of B symptoms (night sweats, fever, weight loss).

Diagnosis

- **Lymph Node Biopsy**: Presence of Reed-Sternberg cells confirms diagnosis.
- **Bone Marrow Biopsy**: Useful for staging in advanced disease.
- **Imaging**: CT, PET scans for staging and response assessment.

Treatment

Stage	Treatment
Early Stage (IA, IIA)	Combined radiotherapy and chemotherapy. Long-term monitoring for secondary malignancies due to radiation exposure.
Advanced Stage (III, IVA/B)	Chemotherapy alone (e.g., ABVD regimen: Adriamycin, Bleomycin, Vincristine, Doxorubicin).
Bulky Disease	Large chest masses may require combined radiotherapy and chemotherapy regardless of stage.
Relapsed Disease	Salvage chemotherapy followed by autologous stem cell transplantation.

Complications of Treatment

- **Bleomycin Toxicity**: Risk of pulmonary fibrosis; monitor with pulmonary function tests and HRCT.
- **Doxorubicin (Adriamycin) Toxicity**: Cardiotoxicity at high doses, although rare in standard regimens.

Prognosis

- **Good Overall Prognosis**: Depends on stage and presence of poor prognostic factors (B symptoms).
- **Poor Prognostic Factors**: B symptoms, advanced staging, lymphocyte-depleted histology.

Hodgkin's vs. Non-Hodgkin's Lymphoma (NHL)

Feature	Hodgkin's Lymphoma (HL)	Non-Hodgkin's Lymphoma (NHL)
Age Group	Younger age	Older age
Lymphadenopathy	Commonly cervical or mediastinal	Peripheral lymphadenopathy is common
Reed-Sternberg Cells	Present	Absent
Extra-Nodal Involvement	Rare	Common

Non-Hodgkin's Lymphoma (NHL) Summary

Definition

- Non-Hodgkin's lymphoma (NHL) includes all types of lymphoma except Hodgkin's, with most cases being of B-cell origin. NHL is a heterogeneous group of lymphoid malignancies with variable presentations and prognoses.

Common Subtypes

1. **Diffuse Large B-Cell Lymphoma (DLBCL)**: Most common aggressive type, usually requires immediate treatment.
2. **Burkitt Lymphoma**: Highly aggressive B-cell lymphoma associated with MYC gene rearrangements, commonly seen in children and young adults.
3. **Follicular Lymphoma**: Common indolent form, slow-growing, often asymptomatic at diagnosis.
4. **Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma**: Often associated with chronic inflammation, especially in gastric MALT with H. pylori infection.
5. **Mantle Cell Lymphoma**: Typically more aggressive, often diagnosed at an advanced stage.

Diagnosis

Diagnostic Tool	Purpose
Excision Biopsy	First-line choice for a definitive diagnosis, providing complete tissue architecture.
Needle Core Biopsy	Alternative if excision is not feasible; provides less tissue, but can still confirm diagnosis.
FISH Testing	Used in high-grade B-cell lymphomas to identify MYC, BCL2, and BCL6 rearrangements.
FDG PET-CT	Important for staging and assessing response to treatment, especially in DLBCL and Burkitt lymphoma.

Management by Subtype

Subtype	Management Strategy
Follicular Lymphoma	- **Asymptomatic**: Observation with "watch and wait." - **Stage IIA**: Local radiotherapy. - **Advanced Stages**: Rituximab-based regimens (e.g., with CVP or CHOP) for symptomatic patients.
MALT Lymphoma	- **H. pylori Positive Gastric MALT**: H. pylori eradication therapy. - **Non-Gastric MALT**: Radiotherapy or chemotherapy with rituximab.
Mantle Cell Lymphoma	- **Advanced Stage, Symptomatic**: Combination chemotherapy (e.g., R-CHOP) with rituximab. - **Stage I or II**: Radiotherapy may be effective in localized disease.

Additional Notes

- **Rituximab**: Commonly used in B-cell NHL, particularly effective when combined with chemotherapy.
- **Watch and Wait**: Commonly used in asymptomatic, indolent forms like follicular lymphoma, where aggressive treatment offers no survival advantage in early stages.
- **H. pylori Eradication in MALT Lymphoma**: Effective in gastric MALT lymphoma, often leads to remission without further therapy.

Burkitt's lymphoma

Definition

- Burkitt's lymphoma is a highly aggressive B-cell non-Hodgkin lymphoma characterized by rapid growth and a high proliferation rate. It is associated with chromosomal translocations involving the MYC gene, leading to uncontrolled cell growth.

Epidemiology

- **Age Group**: Commonly affects children and young adults.
- **Geographical Variants**:
  - **Endemic (African) Burkitt's Lymphoma**: Most common in equatorial Africa and associated with Epstein-Barr virus (EBV).
  - **Sporadic Burkitt's Lymphoma**: Found worldwide, often affecting the abdomen.
  - **Immunodeficiency-Associated Burkitt's Lymphoma**: Common in HIV-positive individuals.

Pathophysiology

- **MYC Translocation**: Chromosomal translocation t(8;14) involving the MYC oncogene on chromosome 8 and the immunoglobulin heavy chain locus on chromosome 14; less commonly, t(2;8) and t(8;22).
- **Epstein-Barr Virus (EBV)**: Strongly associated with endemic Burkitt's lymphoma, EBV infection contributes to B-cell proliferation.

Clinical Features

Variant	Presentation
Endemic (African) Variant	- Commonly involves the jaw or facial bones. - Often presents as a rapidly growing mass in the jaw or orbit.
Sporadic Variant	- Usually presents with an abdominal mass, involving the ileocecal region. - Symptoms of bowel obstruction, GI bleeding, or intussusception in severe cases.
Immunodeficiency-Associated	- Often presents with lymphadenopathy and extranodal involvement. - Associated with HIV/AIDS.

Diagnosis

Test	Findings
Histology	**"Starry Sky" Appearance**: Due to interspersed macrophages among proliferating lymphoma cells.
Immunohistochemistry	Positive for **CD10**, **CD19**, **CD20**, and **BCL6**; high Ki-67 index indicating high proliferative rate.
Genetic Testing	**MYC Translocation**: t(8;14) is most common; confirms diagnosis.
EBV Serology	Especially relevant in endemic cases.
Staging (Imaging)	**CT or PET-CT scans** of the chest, abdomen, and pelvis to assess extent of disease. **Bone marrow biopsy** and lumbar puncture are often performed due to high risk of CNS involvement.

Treatment

Treatment Modality	Description
Chemotherapy	- **Short-Intensive Regimens**: Multi-agent chemotherapy (e.g., cyclophosphamide, vincristine, doxorubicin, methotrexate). - **Hyper-CVAD Regimen**: Alternating high-dose chemotherapy cycles.
Intrathecal Chemotherapy	CNS prophylaxis is essential due to high risk of CNS involvement (e.g., methotrexate, cytarabine).
Immunotherapy	Rituximab (anti-CD20 monoclonal antibody) is often added to chemotherapy regimens.
Supportive Therapy	- **Tumor Lysis Syndrome Prophylaxis**: Aggressive hydration, allopurinol, or rasburicase to manage cell lysis risk. - **Antiviral Prophylaxis**: In immunodeficiency-associated cases, as these patients are often at risk of reactivating infections.

Prognosis

- **Highly Curable**: With intensive chemotherapy, survival rates are high, especially in children.
- **Poor Prognosis in Advanced Disease**: Particularly in patients with CNS involvement or in immunocompromised individuals if untreated.

Key Points for MRCP

1. **"Starry Sky" Appearance** on histology is characteristic.
2. **MYC Translocation (t(8;14))** confirms diagnosis.
3. **CNS Prophylaxis** is critical due to high risk of CNS involvement.
4. **Tumor Lysis Syndrome** is a major risk with treatment initiation due to high proliferation rate.

Leukemia

Definition

- Leukemia is a group of hematologic malignancies originating from the bone marrow, characterized by uncontrolled proliferation of abnormal white blood cells. These abnormal cells infiltrate the bone marrow, blood, and other tissues, leading to impaired hematopoiesis and immune dysfunction.

Types of Leukemia

Type	Subtypes	Description
Acute Myeloid Leukemia (AML)	None specific	Rapidly progressive; affects myeloid precursors, primarily in adults.
Acute Lymphoblastic Leukemia (ALL)	B-cell ALL T-cell ALL	Commonly affects children; involves lymphoid precursors and can infiltrate CNS and lymph nodes.
Chronic Myeloid Leukemia (CML)	Chronic Phase Accelerated Phase Blast Crisis	Slow progression; associated with the Philadelphia chromosome (BCR-ABL fusion gene).
Chronic Lymphocytic Leukemia (CLL)	None specific	Indolent course; affects mature B cells, mainly in older adults, and can involve lymphadenopathy and splenomegaly.

Epidemiology

- **Acute Leukemias (AML, ALL)**: More common in younger patients (ALL is the most common cancer in children), but AML also affects adults.
- **Chronic Leukemias (CML, CLL)**: Generally affect older adults; CLL is the most common leukemia in Western countries.

Clinical Features

Symptom/Sign	Explanation
Anemia	Fatigue, pallor due to decreased red blood cell production.
Infections	Frequent infections due to neutropenia or dysfunctional leukocytes.
Bleeding and Bruising	Thrombocytopenia leading to petechiae, easy bruising, and mucosal bleeding.
Bone Pain	Due to marrow expansion, especially in acute leukemias.
Lymphadenopathy and Splenomegaly	Common in ALL and CLL; indicates infiltration of leukemic cells in lymph nodes and spleen.
Systemic Symptoms	Fever, weight loss, and night sweats are common in chronic leukemias.

Diagnostic Evaluation

Test	Findings
Complete Blood Count (CBC)	Shows leukocytosis, anemia, and thrombocytopenia; blasts in peripheral blood for acute leukemias.
Peripheral Blood Smear	Identifies abnormal cells (blasts in acute leukemias, mature lymphocytes in CLL).
Bone Marrow Biopsy	Confirms diagnosis; blast count ≥20% indicates acute leukemia.

Flow Cytometry	Determines immunophenotype of leukemic cells, distinguishing myeloid from lymphoid leukemias.
Cytogenetic Analysis	Identifies specific chromosomal abnormalities (e.g., Philadelphia chromosome in CML, t(9;22)).
Molecular Testing	BCR-ABL for CML, FLT3 mutation in AML, and other genetic markers for prognosis and therapy choice.

Treatment Overview

Leukemia Type	Treatment Strategy
Acute Myeloid Leukemia (AML)	- **Chemotherapy**: Standard induction with cytarabine and anthracycline. - **Targeted Therapy**: FLT3 inhibitors for FLT3-mutated AML. - **Stem Cell Transplant**: Considered for high-risk or relapsed patients.
Acute Lymphoblastic Leukemia (ALL)	- **Chemotherapy**: Multi-agent regimens. - **CNS Prophylaxis**: Intrathecal chemotherapy to prevent CNS relapse. - **Stem Cell Transplant**: For high-risk or relapsed cases.
Chronic Myeloid Leukemia (CML)	- **Tyrosine Kinase Inhibitors (TKIs)**: Imatinib, dasatinib, or nilotinib as frontline therapy targeting BCR-ABL. - **Stem Cell Transplant**: Reserved for TKI-resistant cases or advanced-phase CML.
Chronic Lymphocytic Leukemia (CLL)	- **Observation**: For asymptomatic, low-risk patients. - **Chemotherapy/Targeted Therapy**: Ibrutinib, venetoclax, or obinutuzumab for symptomatic or progressive disease. - **Stem Cell Transplant**: Rare, for refractory disease.

Complications

- **Infections**: Due to neutropenia and immunosuppression.
- **Tumor Lysis Syndrome**: Especially in acute leukemias post-chemotherapy; requires aggressive hydration and monitoring.
- **Bleeding**: Due to thrombocytopenia, especially in acute leukemias.
- **CNS Involvement**: More common in ALL; may require intrathecal chemotherapy.

Prognosis

Type	Prognostic Factors	General Prognosis
AML	Age, cytogenetics (e.g., FLT3 mutation), initial response to therapy.	Poorer prognosis in older adults.
ALL	Age, genetic markers (e.g., Philadelphia chromosome), initial WBC count.	Children have a high cure rate (>80%).
CML	Response to TKIs, phase at diagnosis (chronic vs. blast crisis).	Excellent with TKI therapy in chronic phase.
CLL	Cytogenetics (e.g., del(17p)), IGHV mutation status, age.	Variable; indolent cases may have a normal lifespan.

Key Points for MRCP

1. **Blasts in Peripheral Blood**: Indicates acute leukemia.
2. **Philadelphia Chromosome**: Pathognomonic for CML; BCR-ABL testing guides TKI therapy.
3. **CNS Prophylaxis in ALL**: Required due to high CNS relapse risk.
4. **Differentiation**: CLL is characterized by mature lymphocytes, while ALL involves immature lymphoid precursors.

Differences Between AML, ALL, CML, and CLL

Feature	Acute Myeloid Leukemia (AML)	Acute Lymphoblastic Leukemia (ALL)	Chronic Myeloid Leukemia (CML)	Chronic Lymphocytic Leukemia (CLL)
Definition	Malignancy of myeloid precursor cells in the bone marrow.	Malignancy of lymphoid precursor cells in bone marrow.	Clonal proliferation of myeloid cells with BCR-ABL fusion gene.	Malignancy of mature B lymphocytes.
Age Group	Primarily affects adults, typically >60 years.	Most common in children (ages 2–5), but also seen in adults.	Primarily affects adults, typically 40–60 years.	Primarily older adults (>60 years); rare in young adults.
Onset and Course	Rapid onset, aggressive course.	Rapid onset, aggressive course.	Slow onset, chronic and indolent course.	Slow, often asymptomatic or indolent course.
Clinical Features	- Fatigue, pallor (anemia) - Infections (neutropenia) - Bleeding (thrombocytopenia) - Bone pain	- Fatigue, pallor - Infections, fever - Bone/joint pain (common in children) - Lymphadenopathy	- Fatigue, weight loss - Splenomegaly - Often asymptomatic initially	- Often asymptomatic - Fatigue, lymphadenopathy, splenomegaly - Recurrent infections
Blood Smear Findings	**Blasts** with Auer rods (myeloid lineage markers).	**Blasts** (lymphoid lineage markers).	Increased mature myeloid cells, <5% blasts.	Increased mature lymphocytes (smudge cells on smear).
Bone Marrow Findings	>20% myeloblasts in bone marrow.	>20% lymphoblasts in bone marrow.	Hypercellular marrow with granulocytic proliferation.	Hypercellular marrow with increased mature lymphocytes.

Feature	Acute Myeloid Leukemia (AML)	Acute Lymphoblastic Leukemia (ALL)	Chronic Myeloid Leukemia (CML)	Chronic Lymphocytic Leukemia (CLL)
Genetic Abnormalities	Common mutations: FLT3, NPM1, CEBPA.	Common mutations: t(12;21), t(9;22) (Philadelphia chromosome in adult ALL).	**Philadelphia chromosome** t(9;22), BCR-ABL fusion gene.	Deletion of 13q, 17p, or 11q; trisomy 12.
Prognostic Factors	Age, cytogenetics (e.g., FLT3 mutation), initial response to therapy.	Age, cytogenetics (e.g., Philadelphia chromosome), WBC count at diagnosis.	BCR-ABL mutation response to tyrosine kinase inhibitors (TKIs).	Cytogenetic abnormalities, IGHV mutation status, age.
First-Line Treatment	**Chemotherapy** (e.g., cytarabine, anthracycline).	**Chemotherapy** with CNS prophylaxis (intrathecal).	**Tyrosine Kinase Inhibitors** (TKIs) like imatinib.	**Observation** if asymptomatic; targeted therapy (e.g., ibrutinib) for symptoms.
Stem Cell Transplant	For high-risk or relapsed cases.	For high-risk or relapsed cases, particularly adults.	Reserved for TKI-resistant cases or advanced phase.	Rarely used, considered in refractory cases.
Prognosis	Poorer in older adults; depends on genetics and response to therapy.	High cure rate in children (>80%); lower in adults.	Excellent with TKI therapy in chronic phase.	Variable; indolent cases have good prognosis; aggressive cases have poorer outcomes.

Hairy cell leukaemia (HCL)

Feature	Description
Definition	Rare, chronic B-cell lymphoproliferative disorder characterized by abnormal B lymphocytes with "hairy" cytoplasmic projections.
Epidemiology	- Typically affects middle-aged to older adults (median age: 50–55 years). - More common in males (M ratio ~ 4:1).
Pathophysiology	- Clonal proliferation of B cells in the bone marrow and spleen. - Cells exhibit unique "hairy" cytoplasmic projections.
Clinical Features	- **Pancytopenia**: Leads to fatigue, recurrent infections, and bleeding/bruising. - **Splenomegaly**: Common and often massive, causing abdominal discomfort. - **Absence of Lymphadenopathy**: Rarely present.
Diagnosis	- **Peripheral Blood Smear**: Shows characteristic "hairy" B cells. - **Bone Marrow Biopsy**: Confirms diagnosis, showing infiltrates of hairy cells with fibrosis ("dry tap"). - **Immunophenotyping**: Positive for CD19, CD20, CD22, CD103, and CD11c markers. - **BRAF V600E Mutation**: Present in most cases, useful for confirmation.
Laboratory Findings	- **Pancytopenia**: Anemia, neutropenia, and thrombocytopenia. - **Monocytopenia**: Common in HCL. - **Serum Markers**: Increased beta-2-microglobulin.
Treatment	- **First-Line Therapy**: Purine analogs (cladribine or pentostatin) lead to long-term remission. - **BRAF Inhibitors** (e.g., vemurafenib): Used for relapsed/refractory cases with confirmed BRAF V600E mutation. - **Rituximab**: Monoclonal antibody therapy for relapsed or refractory HCL. - **Splenectomy**: Rarely needed, but may relieve symptoms in cases of massive splenomegaly.
Prognosis	- Generally good with appropriate treatment; high rates of remission with purine analogs. - Median survival exceeds 10 years. - Relapses may occur, but further treatment is typically effective.

Systemic Mastocytosis (SM)

Definition

- A **myeloproliferative disorder** characterized by **abnormal mast cell proliferation and accumulation** in tissues such as bone marrow, skin, liver, spleen, and gastrointestinal tract.

Classification (WHO Criteria)

1. **Cutaneous Mastocytosis**: Limited to the skin.
2. **Indolent SM**: Most common; slow progression.
3. **Smoldering SM**: Intermediate severity.
4. **Aggressive SM**: Involves organ dysfunction without mast cell leukemia.
5. **Mast Cell Leukemia**: Rare, severe form.
6. **SM with Associated Hematologic Neoplasm**: Coexisting hematologic malignancy.

Pathophysiology

- Caused by activating mutations in the **KIT gene** (e.g., KIT D816V mutation).
- Excessive **mast cell degranulation** releases histamine, tryptase, and other mediators.

Clinical Features

- **Skin**:
  - Urticaria pigmentosa (brown macules or papules).
  - Pruritus, flushing.
- **Systemic Symptoms**:
  - Fatigue, weight loss, fever.
  - Anaphylaxis (triggered by physical stimuli or allergens).
- **Gastrointestinal**:
  - Abdominal pain, diarrhea, nausea.
  - Malabsorption.
- **Bone and Joint**:
  - Osteoporosis, fractures.
  - Bone pain.
- **Other**:
  - Hepatosplenomegaly, lymphadenopathy.

Diagnosis

- **Major Criteria**:
  - Dense mast cell infiltrates in bone marrow or other extracutaneous organs.
- **Minor Criteria** (need ≥2):
  - Elevated **serum tryptase** (>20 ng/mL).
  - Detection of **KIT D816V mutation**.
  - Abnormal mast cell morphology.
  - CD25 and/or CD2 expression on mast cells.

Management

- **Symptom Control**:
  - **Antihistamines** (H1/H2 blockers): For flushing, pruritus.
  - **Cromolyn sodium**: Stabilizes mast cells.
  - **Epinephrine**: For anaphylaxis.
- **Targeted Therapy**:
  - **Midostaurin** (KIT inhibitor): For advanced SM.

- **Bone Health**:
  - Bisphosphonates for osteoporosis.
- **Advanced Disease**:
  - Cytoreductive therapies: **Cladribine**, **interferon-alpha**.
  - Stem cell transplant in select cases.

Prognosis

- Depends on subtype:
  - **Indolent SM**: Good prognosis, normal life expectancy.
  - **Aggressive SM** or **mast cell leukemia**: Poor prognosis.

Key Points

- **KIT mutations** are central to pathogenesis.
- Diagnosis relies on **bone marrow biopsy** and **serum tryptase levels**.

Multiple myeloma (MM)

Definition

- Multiple myeloma is a neoplasm of bone marrow plasma cells characterized by monoclonal protein production, bone lesions, and immunodeficiency.

Epidemiology

- **Peak Incidence**: 60-70 years.
- **Most Common**: Primary bone tumor in individuals over 50 years.
- **Demographics**: Equal sex ratio, more common in Afro-Caribbean populations than Caucasians.

Diagnostic Criteria

- Diagnosis requires either one major criterion and one minor criterion or three minor criteria.

Criteria	Description
Major Criteria	- Plasmacytoma on biopsy. - ≥30% plasma cells in bone marrow. - Elevated monoclonal (M) protein: IgG or IgA in serum, or Bence Jones protein in urine.
Minor Criteria	- 10-30% plasma cells in bone marrow. - Minor M protein elevation. - Osteolytic lesions on imaging. - Hypogammaglobulinemia.

Investigations

Purpose	Tests
To Confirm Paraprotein	- **Serum Protein Electrophoresis (SPEP)** (initial test). - **Serum Free Light Chain Assay**. - **Serum Immunofixation** if SPEP is abnormal.
For Myeloma Diagnosis	- **Bone Marrow Aspirate & Biopsy**: Confirms >10% plasma cells. - **Morphology & Flow Cytometry** to assess plasma cell phenotype.
Spinal Cord Compression	- **Urgent MRI** for spine if suspected, before definitive myeloma testing.

Treatment Overview

1. **Asymptomatic Patients**: "Watch and wait" unless ≥60% clonal cells, high free light chain ratio, or ≥1 bone lesion.
2. **Symptomatic Patients**:
   - **HCT Eligible**: Chemotherapy induction (e.g., bortezomib, dexamethasone), followed by autologous hematopoietic cell transplantation (HCT).
   - **HCT Ineligible**: Combination chemotherapy (e.g., dexamethasone with lenalidomide).
3. **Supportive Therapy**:
   - **Osteolysis and Bone Pain**: Bisphosphonates, radiotherapy.
   - **Pancytopenia**: Blood transfusions, G-CSF, erythropoietin.
   - **Hyperviscosity Syndrome**: Plasma exchange, chemotherapy for disease control.

Specific Treatment Protocols

Condition	Treatment
Newly Diagnosed (Transplant Eligible)	- Bortezomib + dexamethasone, or - Bortezomib + dexamethasone + thalidomide.
Newly Diagnosed (Transplant Ineligible)	- Thalidomide + alkylating agent + corticosteroid.
First Relapse	- Bortezomib monotherapy if previous therapy was single-agent.
Multiple Prior Therapies	- Lenalidomide + dexamethasone.
Myeloma-Induced Renal Disease	- Bortezomib + dexamethasone, or if unsuitable, thalidomide + dexamethasone. - Avoid plasma exchange.

Managing Complications

Complication	Management
Bone Disease	- Routine bisphosphonates (e.g., zoledronic acid, pamidronate) to reduce fractures and modulate disease.
Peripheral Neuropathy	- Modify bortezomib regimen: switch to subcutaneous, reduce dose/frequency. - Hold neurotoxic agents if severe neuropathy.
Fatigue	- Erythropoietin analogues to maintain hemoglobin at 110–120 g/L.
Spinal Cord Compression	- Urgent IV steroids and localized radiotherapy. Vertebroplasty if vertebral instability without cord compression.

Prognosis

- **Prognostic Indicators**: High β2-microglobulin, low albumin, and elevated LDH indicate poor prognosis.
- **International Staging System**:

Stage	Criteria	Median Survival (Months)
I	β2-microglobulin < 3.5 mg/L, Albumin > 35 g/L	62
II	Not Stage I or III	45
III	β2-microglobulin > 5.5 mg/L	29

Key Points for MRCP

1. **Beta-2 Microglobulin**: Critical for prognosis; higher levels indicate greater disease burden.
2. **M Protein and Bence Jones Proteins**: Key diagnostic markers, found in serum and urine.
3. **Bone Lesions and Hypercalcemia**: Common complications due to osteolytic activity.
4. **Myeloma Treatment**: Based on symptom severity, transplant eligibility, and response to first-line therapies.

Pathophysiology

- Neoplasm of the bone marrow plasma cells → Bone marrow infiltration → cytopenia + osteolysis → hypercalcemia
- Overproduction of monoclonal immunoglobulin and/or light chains → Non-functioning antibodies → functional antibody deficiency + ↑ Serum viscosity → hyperviscosity syndrome, organ deposition (renal failure , carpal tunnel)

Features

Classic symptoms of multiple myeloma:

1. Bone pain
2. Pathological fracture
3. Anaemia and
4. Hypercalcaemia

Lab findings

- ↑ total protein (globulin component)
- Hypercalcaemia
- To confirm the presence of a paraprotein → best initial test → serum electrophoresis
- To confirm a diagnosis of myeloma → bone marrow aspirate and trephine biopsy → dark red jelly-like material in the syringe (Plasma cells)

Treatment

- Initial → chemotherapy induction.
- Patients with high paraprotein levels + hyperviscosity symptoms → urgent plasma exchange
- Patients presenting with spinal cord compression → I.V Steroids immediately + Urgent spinal MRI (the treatment of choice is local radiotherapy.)
- B2-microglobulin is a useful marker of prognosis

Laboratory confirmation of Multiple Myeloma (NICE 2018)

1. To confirm the presence of a paraprotein indicating possible myeloma or (MGUS):
   - Two tests must always be done: both serum electrophoresis and either serum or urinary free light chains
   - If serum protein electrophoresis is abnormal, use serum immunofixation to confirm the presence of a paraprotein indicating possible myeloma or MGUS.
   - Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma.
     - ☞ free light chains (20–30% of cases of myeloma) are found in the absence of a detectable monoclonal protein in the peripheral blood.
2. To confirm a diagnosis of myeloma:
   - Bone marrow aspirate and trephine biopsy
     - ☞ Morphology to determine plasma cell percentage (≥10%).
     - ☞ flow cytometry to determine plasma cell phenotype.

Monoclonal gammopathy of undetermined significance (MGUS)

Definition

- MGUS is a condition in which an abnormal monoclonal (M) protein is produced by plasma cells in the bone marrow, without evidence of malignancy or symptoms. It is typically asymptomatic but has a small risk of progression to multiple myeloma or other plasma cell disorders.

Pathophysiology

- **Monoclonal Protein Production**: A small population of plasma cells produces an abnormal M protein, detected in the blood. Unlike multiple myeloma, MGUS does not cause significant organ or tissue damage.
- **Risk of Progression**: MGUS has an annual progression risk of about 1% to multiple myeloma, Waldenström's macroglobulinemia, or other lymphoproliferative disorders.

Clinical Features

- **Asymptomatic**: Most patients have no symptoms.
- **Incidental Finding**: Often detected on routine blood tests due to an elevated total protein level or abnormal serum protein electrophoresis (SPEP).

Diagnosis Criteria

- **Serum M Protein Level**: <3 g/dL (higher levels suggest multiple myeloma).
- **Bone Marrow Plasma Cells**: <10% monoclonal plasma cells in the bone marrow.
- **Absence of CRAB Features**: No evidence of hypercalcemia, renal impairment, anemia, or bone lesions (CRAB criteria).

Test	Findings/Implications
Serum Protein Electrophoresis (SPEP)	Detects and quantifies the M protein.
Immunofixation Electrophoresis	Confirms the type of monoclonal protein (e.g., IgG, IgA, or IgM subtype).
Serum Free Light Chain Assay	Assesses the kappa-to-lambda light chain ratio, which may indicate an increased risk of progression.
Bone Marrow Biopsy	Usually not required unless there is suspicion of progression to myeloma or another malignancy.

Types of MGUS

1. **Non-IgM MGUS**: Most common type, can progress to multiple myeloma.
2. **IgM MGUS**: Higher risk of progressing to Waldenström's macroglobulinemia or lymphoma.
3. **Light Chain MGUS**: Only light chains are elevated, with risk of progression to light chain multiple myeloma or amyloidosis.

Management

- **Observation and Monitoring**: MGUS is typically managed with regular follow-up rather than treatment.
  - **Frequency of Follow-up**: Every 6–12 months with SPEP, complete blood count (CBC), serum calcium, creatinine, and serum free light chains.
  - **Monitoring for Progression**: Look for development of CRAB features or a significant rise in M protein levels.
- **Risk Stratification**:
  - **Low-Risk MGUS**: IgG subtype, M protein <1.5 g/dL, normal free light chain ratio.

- **High-Risk MGUS**: IgA or IgM subtype, M protein >1.5 g/dL, abnormal free light chain ratio.

Prognosis

- **Low Overall Progression Rate**: About 1% per year progression to multiple myeloma or related malignancies.
- **Long-Term Monitoring Needed**: Patients need regular monitoring to detect signs of progression, especially those at higher risk.

Key Points for MRCP

1. **Asymptomatic Condition**: MGUS lacks the CRAB features seen in multiple myeloma.
2. **Annual Risk of Progression**: Approximately 1% per year; higher risk with non-IgG subtypes, high M protein levels, and abnormal free light chain ratio.
3. **No Immediate Treatment**: Management involves regular monitoring and assessment for signs of progression.
4. **Differentiation from Myeloma**: MGUS has M protein <3 g/dL, <10% plasma cells in bone marrow, and no CRAB symptoms.

feature	MGUS	myeloma
M protein concentration in serum	<30 g/l	>30 g/l
bone marrow plasma cells	<10 %	>10 %
organ and tissue impairment	no end organ damage including bone lesions	organ or tissue impairment (including bone lesions)

Thymoma

Definition

- Thymoma is a rare tumor originating from the epithelial cells of the thymus gland, often associated with autoimmune conditions such as myasthenia gravis. Thymomas are typically slow-growing and can be benign or malignant.

Classification

1. **Non-Invasive Thymoma**: Confined to the thymus, does not spread.
2. **Invasive Thymoma**: Invades surrounding tissues, including the pericardium, lungs, and major blood vessels.

Pathophysiology

- **Tumor Origin**: Arises from thymic epithelial cells.
- **Autoimmune Association**: Thymomas are frequently linked with autoimmune diseases, most notably myasthenia gravis (present in up to 30–50% of patients with thymoma). Other associated conditions include red cell aplasia, hypogammaglobulinemia, and systemic lupus erythematosus (SLE).

Clinical Features

- **Asymptomatic**: Many thymomas are found incidentally during imaging.
- **Symptoms due to Mass Effect**:
  - **Chest Pain**: Pressure on surrounding structures.
  - **Dyspnea**: Compression of airways or pleura.
  - **Cough**: If the trachea or bronchi are affected.
- **Systemic Symptoms**: Fatigue, weakness, especially if associated with myasthenia gravis (ptosis, muscle weakness).
- **Paraneoplastic Syndromes**: Myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia.

Diagnosis

Test	Findings
Chest CT Scan	Primary imaging for detection, size, and extent; assesses invasion into surrounding structures.
MRI	Useful for determining the relationship with adjacent vessels and structures.
Biopsy	Necessary to confirm diagnosis if imaging is inconclusive or if surgery is not initially indicated.
Autoimmune Panel	For associated autoimmune diseases (e.g., acetylcholine receptor antibodies for myasthenia gravis).

Staging (Masaoka-Koga Classification)

- **Stage I**: Tumor encapsulated and confined to the thymus.
- **Stage II**: Invasion into surrounding fatty tissue or mediastinal pleura.
- **Stage III**: Invasion into nearby organs (e.g., pericardium, great vessels).
- **Stage IV**: Distant metastasis (e.g., lungs, liver).

Treatment

Stage	Management Strategy
Stage I (Localized)	- **Surgical Resection**: Complete removal of the tumor.
Stage II-III (Locally Invasive)	- **Surgery**: Radical thymectomy to remove the tumor and affected surrounding tissue. - **Radiation Therapy**: Postoperative for local control if margins are positive or if the tumor is invasive.
Stage IV (Metastatic)	- **Chemotherapy**: Platinum-based chemotherapy (e.g., cisplatin, doxorubicin) for advanced or recurrent disease. - **Radiation**: Palliative for metastatic disease.
Associated Myasthenia Gravis	- **Anticholinesterase Inhibitors** (e.g., pyridostigmine) to manage symptoms. - **Immunosuppressive Therapy** may be necessary for symptom control.

Key Points

1. **Association with Myasthenia Gravis**: Strongly linked with thymoma; testing for acetylcholine receptor antibodies is recommended.
2. **Surgical Resection**: Primary treatment for non-invasive and invasive thymomas.
3. **Masaoka-Koga Staging**: Guides prognosis and management.
4. **Radiation and Chemotherapy**: Used postoperatively for invasive thymomas or in metastatic disease.

Tumour lysis syndrome (TLS)

Pathophysiology

- **Trigger:** TLS typically occurs after chemotherapy or radiotherapy, particularly in high-grade hematologic malignancies like leukemia and lymphoma.
- **Mechanism:** Rapid breakdown of tumor cells leads to the release of intracellular contents:
  - **High Potassium**: Can cause cardiac arrhythmias.
  - **High Phosphate**: Leads to calcium phosphate deposition in tissues.
  - **High Uric Acid**: Risk of uric acid crystal formation in kidneys, causing acute kidney injury (AKI).
  - **Low Calcium**: Secondary to phosphate binding, potentially leading to neuromuscular irritability.

Diagnostic Criteria

- **Laboratory TLS**: Defined by at least two of the following within three days before or seven days after chemotherapy:
  - Uric acid > 8 mg/dL
  - Potassium > 6 mmol/L
  - Phosphate > 4.5 mg/dL
  - Calcium < 7 mg/dL
- **Clinical TLS**: Laboratory TLS with one or more clinical complications (e.g., renal failure, cardiac arrhythmias, seizures).

Management

Management Step	Description
Aggressive Hydration	- Aim for **3 L/m²/day** to enhance renal clearance of uric acid and other metabolites.
Electrolyte Management	- **Hyperkalemia**: Use IV calcium gluconate, insulin with glucose, or potassium binders. - **Hyperphosphatemia**: Phosphate binders (e.g., sevelamer) if levels are high. - **Hypocalcemia**: Treat only if symptomatic, as calcium supplementation may worsen phosphate deposition.
Uric Acid Control	- **IV Rasburicase**: Enzyme that breaks down uric acid; indicated for high-risk cases. - **Allopurinol**: Alternative in moderate-risk patients to prevent uric acid formation, but does not reduce existing uric acid levels.
Renal Replacement Therapy (RRT)	- Indicated for **severe oliguria or anuria, persistent hyperkalemia**, or **symptomatic hypocalcemia** due to high phosphate.

Prevention

- **High-Risk Patients**: Administer IV rasburicase before and during the first days of chemotherapy to rapidly reduce uric acid levels.
- **Moderate-Risk Patients**: IV allopurinol may be given to inhibit uric acid production, especially when rasburicase is unavailable.

Waldenström's Macroglobulinemia (WM)

Definition

- Waldenström's macroglobulinemia (WM) is a rare type of non-Hodgkin lymphoma characterized by the overproduction of monoclonal IgM antibodies by malignant lymphoplasmacytic cells, leading to symptoms related to hyperviscosity, anemia, and organ infiltration.

Pathophysiology

- **Clonal B-Cell Disorder**: Arises from lymphoplasmacytic cells in the bone marrow, which produce monoclonal IgM.
- **Genetic Mutations**: Commonly associated with MYD88 L265P mutation in >90% of cases, and CXCR4 mutations in some patients, which influence disease behavior and response to therapy.

Clinical Features

- **Hyperviscosity Syndrome**: Due to high IgM levels, leading to blurred vision, headaches, dizziness, and retinal hemorrhages.
- **Anemia**: Fatigue and pallor are common due to bone marrow infiltration.
- **Organomegaly**: Splenomegaly, hepatomegaly, and lymphadenopathy can occur due to infiltration.
- **Neuropathy**: Peripheral neuropathy caused by IgM binding to myelin.
- **Cryoglobulinemia and Cold Sensitivity**: Cold-induced pain, Raynaud's phenomenon, and digital ulcers due to cryoglobulins.
- **Bleeding Tendency**: May result from platelet dysfunction or acquired von Willebrand disease.

Diagnosis

Test	Findings/Implications
Complete Blood Count (CBC)	Shows anemia, sometimes with leukopenia or thrombocytopenia if bone marrow is heavily infiltrated.
Serum Protein Electrophoresis (SPEP)	Detects the presence of monoclonal IgM spike.
Immunofixation	Confirms monoclonal IgM protein in the serum.
Quantitative Immunoglobulins	Elevated IgM with low levels of IgG and IgA (immunodeficiency).
Bone Marrow Biopsy	Shows lymphoplasmacytic infiltrate, often with MYD88 mutation.
MYD88 and CXCR4 Mutation Testing	Assists in confirming diagnosis and guiding treatment.
Serum Viscosity	Assessed if hyperviscosity syndrome is suspected.

Treatment

Condition/Stage	Treatment Options
Asymptomatic (Smoldering)	Observation without immediate treatment.
Symptomatic WM	- **Plasmapheresis**: Urgent for hyperviscosity symptoms to rapidly reduce IgM levels. - **Rituximab**: Anti-CD20 monoclonal antibody; often combined with other agents. - **Chemotherapy**: Bendamustine, cyclophosphamide. - **Targeted Therapy**: Ibrutinib, especially effective for patients with MYD88 mutation.
Relapsed/Refractory WM	Consider second-line therapies like proteasome inhibitors (e.g., bortezomib), novel BTK inhibitors, or participation in clinical trials.

Prognosis

- **Variable**: Depends on age, disease burden, and symptoms. The median survival is around 5–10 years, with newer therapies improving outcomes.
- **Prognostic Factors**: Elevated β2-microglobulin, low hemoglobin, high IgM, and advanced age are associated with poorer prognosis.

Key Points for MRCP

1. **IgM Monoclonal Spike**: Distinguishes WM from multiple myeloma, which commonly involves IgG or IgA.
2. **Hyperviscosity Syndrome**: Requires urgent plasmapheresis for symptomatic relief.
3. **MYD88 Mutation**: Present in most WM cases and guides treatment decisions, especially for ibrutinib use.
4. **Peripheral Neuropathy**: Common in WM, can be exacerbated by IgM monoclonal proteins affecting nerves.

Tumour markers

Tumor Marker	Associated Cancers	Clinical Utility
AFP (Alpha-Fetoprotein)	- Hepatocellular carcinoma (HCC) - Germ cell tumors (non-seminomatous, yolk sac)	- Diagnosis and monitoring of HCC. - Evaluating germ cell tumors.
CA-125	- Ovarian cancer (especially epithelial type) - Endometrial cancer	- Monitoring treatment response and recurrence in ovarian cancer. - Not specific for diagnosis but useful in follow-up.
CA 19-9	- Pancreatic cancer - Cholangiocarcinoma - Gastric cancer	- Monitoring pancreatic cancer progression. - Less useful for diagnosis due to low specificity.
CA 15-3 / CA 27-29	- Breast cancer	- Monitoring metastatic breast cancer response to treatment. - Not specific or reliable for diagnosis.

Tumor Marker	Associated Cancers	Clinical Utility
CEA (Carcinoembryonic Antigen)	- Colorectal cancer - Pancreatic, gastric, breast, and lung cancers	- Monitoring for recurrence in colorectal cancer post-treatment. - Can be elevated in benign conditions, so not specific for diagnosis.
hCG (Human Chorionic Gonadotropin)	- Testicular cancer (non-seminomatous) - Choriocarcinoma - Trophoblastic disease	- Diagnosing and monitoring testicular and trophoblastic tumors. - Elevated in pregnancy, so interpretation requires context.
PSA (Prostate-Specific Antigen)	- Prostate cancer - Benign prostatic hyperplasia (BPH)	- Screening and monitoring prostate cancer. - Can be elevated in BPH or prostatitis, limiting specificity.
Thyroglobulin	- Thyroid cancer (especially differentiated thyroid cancer)	- Monitoring for recurrence of thyroid cancer post-thyroidectomy. - Only useful if patient has had thyroid removed.
Calcitonin	- Medullary thyroid cancer	- Diagnostic and follow-up marker for medullary thyroid carcinoma. - Used to screen for recurrence post-surgery.
LDH (Lactate Dehydrogenase)	- Germ cell tumors - Lymphomas - Melanoma	- Prognostic marker in testicular cancer and lymphoma. - High levels indicate tumor burden or aggressive disease.
S-100	- Melanoma - Neural tumors (e.g., schwannoma)	- Monitoring and prognosis in melanoma. - Limited utility in initial diagnosis.
β2-Microglobulin	- Multiple myeloma - Lymphoma	- Prognosis and disease monitoring in multiple myeloma and some lymphomas. - Also elevated in renal disease.
Neuron-Specific Enolase (NSE)	- Small cell lung cancer - Neuroendocrine tumors	- Monitoring response to treatment in small cell lung cancer. - Elevated in other neuroendocrine tumors as well.
BCR-ABL	- Chronic myeloid leukemia (CML)	- Diagnostic marker for CML. - Used to monitor response to targeted therapy (e.g., tyrosine kinase inhibitors).
HER2/neu	- Breast cancer - Gastric cancer	- Determines eligibility for HER2-targeted therapies (e.g., trastuzumab). - Prognostic marker in HER2-positive breast cancer.

Breast cancer

Definition

- Breast cancer is a malignant tumor that originates in the breast tissue, most commonly in the ducts or lobules. It is one of the most common cancers in women, though it can also occur in men.

Types

1. **Ductal Carcinoma In Situ (DCIS)**: Non-invasive, confined to the ducts.
2. **Invasive Ductal Carcinoma (IDC)**: Most common type, begins in the ducts and invades surrounding tissue.
3. **Invasive Lobular Carcinoma (ILC)**: Begins in the lobules and can spread to other areas.
4. **Triple-Negative Breast Cancer**: Lacks estrogen, progesterone, and HER2 receptors, often more aggressive.
5. **HER2-Positive Breast Cancer**: Overexpresses HER2 protein, responds to targeted therapy.

Risk Factors

- **Genetic**: BRCA1 and BRCA2 mutations, family history.
- **Hormonal**: Early menarche, late menopause, hormone replacement therapy, nulliparity.
- **Lifestyle**: Obesity, alcohol consumption, smoking, sedentary lifestyle.

Clinical Features

- **Breast Lump**: Typically painless, firm, and irregular.
- **Skin Changes**: Dimpling, redness, or changes resembling orange peel (peau d'orange).
- **Nipple Changes**: Discharge (especially bloody), inversion, or scaling.
- **Axillary Swelling**: Lymph node involvement may cause underarm swelling.

Diagnosis

Test	Purpose/Findings
Clinical Examination	Palpation of breast, axilla, and supraclavicular areas to assess lump characteristics and lymph nodes.
Imaging	- **Mammography**: Primary screening tool for breast cancer. - **Ultrasound**: Differentiates cystic from solid masses. - **MRI**: High-risk patients or dense breast tissue.
Biopsy	Core needle biopsy for histological confirmation and receptor status testing (ER, PR, HER2).
Receptor Testing	Determines hormone receptor (ER, PR) and HER2 status to guide treatment.
Tumour marker	**CA15-3 tumour marker are used to assess disease activity in metastatic breast cancer**

Staging (TNM Classification)

- **T**: Tumor size (T1–T4).
- **N**: Nodal involvement (N0–N3).
- **M**: Metastasis (M0 or M1).

Stages range from **Stage 0** (in situ) to **Stage IV** (metastatic disease).

Treatment

Stage	Management Strategy
Stage 0 (DCIS)	- **Surgery**: Lumpectomy or mastectomy. - **Radiation Therapy**: Often after lumpectomy.
Early-Stage (I-II)	- **Surgery**: Lumpectomy with radiation or mastectomy. - **Adjuvant Therapy**: Hormonal therapy for hormone receptor-positive tumors (tamoxifen or aromatase inhibitors). - **Chemotherapy**: Based on tumor characteristics and patient risk.
Locally Advanced (III)	- **Neoadjuvant Chemotherapy**: Shrinks the tumor before surgery. - **Surgery**: Mastectomy or breast-conserving surgery. - **Radiation Therapy**: Post-surgical, especially with lymph node involvement.
Metastatic (Stage IV)	- **Hormone Therapy**: For hormone receptor-positive tumors. - **Targeted Therapy**: HER2-targeted therapies (e.g., trastuzumab) for HER2-positive cancer. - **Chemotherapy**: For hormone-refractory or triple-negative breast cancer. - **Palliative Care**: Symptom management and quality-of-life support.

Prognosis

- **Early Stages**: Excellent prognosis with high 5-year survival rates (up to 99% for localized disease).
- **Advanced Stages**: Survival rates decrease with stage; however, treatment advancements have improved outcomes in metastatic disease.

Key Points for MRCP

1. **Screening**: Mammography is recommended for early detection in women over 50 or those with a high-risk profile.
2. **Receptor Status**: Determines eligibility for hormone therapy (ER/PR) and HER2-targeted therapy.
3. **Triple-Negative Breast Cancer**: Typically more aggressive with limited treatment options, requiring chemotherapy.
4. **Staging and Treatment**: Guided by TNM classification and receptor status, ranging from localized surgery to systemic therapy for metastatic disease.

Testicular cancer

Definition

- Testicular cancer is a malignant tumor that originates in the testicles, primarily affecting young men aged 15–35. It is highly curable, especially if detected early.

Types

- **Germ Cell Tumors (95%)**:
  - **Seminomas**: Grow slowly, generally respond well to radiation.
  - **Non-Seminomas**: More aggressive; include subtypes such as embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma.
- **Non-Germ Cell Tumors**:
  - **Leydig Cell Tumors** and **Sertoli Cell Tumors**: Rare, typically benign, but can sometimes secrete hormones.

Risk Factors

- **Cryptorchidism** (undescended testicle)
- **Family History** of testicular cancer
- **Personal History** of testicular cancer
- **Genetic Conditions** (e.g., Klinefelter syndrome)

Clinical Features

- **Painless Testicular Mass**: Most common presentation; typically hard and irregular.
- **Discomfort or Heaviness**: In the scrotum or lower abdomen.
- **Gynecomastia**: Rarely, due to hormone secretion by the tumor.
- **Metastatic Symptoms**: Back pain, cough, or weight loss if metastasized.

Diagnosis

Test	Purpose/Findings
Physical Examination	Palpation of the testes for lumps or irregularities.
Scrotal Ultrasound	Primary imaging modality; helps differentiate between solid and cystic masses.
Tumor Markers	Elevated in many cases of testicular cancer: - **Alpha-Fetoprotein (AFP)**: Elevated in non-seminomas. - **Beta-Human Chorionic Gonadotropin (β-hCG)**: Elevated in both seminomas and non-seminomas. - **Lactate Dehydrogenase (LDH)**: Can be elevated in advanced cases.
CT Scan of Abdomen and Pelvis	To assess for metastasis to retroperitoneal lymph nodes.
Chest CT/X-Ray	To detect pulmonary metastasis in advanced cases.
Orchiectomy	Surgical removal of the affected testicle; both diagnostic and therapeutic.

Staging (TNM Classification)

Stage	Description
Stage I	Limited to the testis.
Stage II	Spread to retroperitoneal lymph nodes.
Stage III	Spread beyond retroperitoneal nodes, potentially involving lungs or other organs.

Treatment

Type	Management Strategy
Stage I Seminoma	- **Radical Orchiectomy**: Primary treatment. - **Surveillance** or adjuvant radiation therapy or chemotherapy based on risk factors.
Stage I Non-Seminoma	- **Radical Orchiectomy**. - **Surveillance** or adjuvant chemotherapy (e.g., BEP: bleomycin, etoposide, cisplatin) for high-risk features.
Stage II/III	- **Radical Orchiectomy** plus **chemotherapy** (e.g., BEP regimen) for advanced cases. - **Retroperitoneal Lymph Node Dissection (RPLND)**: For non-seminoma with persistent lymph node disease after chemotherapy.

Chemotherapy Regimens

- **BEP (Bleomycin, Etoposide, Cisplatin)**: Common for advanced-stage disease.
- **EP (Etoposide, Cisplatin)**: Used for patients with contraindications to bleomycin.

Prognosis

- **Excellent Overall**: 5-year survival rates >95% for early-stage disease.
- **Advanced Disease**: High cure rates with chemotherapy and appropriate surgical management.

Key Points for MRCP

1. **Germ Cell Tumors** are the most common type of testicular cancer, with seminomas and non-seminomas as main subtypes.
2. **Tumor Markers** (AFP, β-hCG, LDH) are essential for diagnosis, staging, and monitoring treatment response.
3. **Radical Orchiectomy** is both diagnostic and therapeutic.
4. **BEP Chemotherapy Regimen** is standard for advanced-stage or metastatic disease.

Von Hippel-Lindau syndrome (VHL)

Definition

- Von Hippel-Lindau syndrome is an autosomal dominant genetic disorder characterized by the formation of multiple benign and malignant tumors due to mutations in the VHL gene, a tumor suppressor gene on chromosome 3p25.5.

Etiology

- **Genetic Mutation**: Mutation in the VHL gene leads to the overactivation of hypoxia-inducible factors (HIF), which promote tumor growth and angiogenesis.

Clinical Features

Manifestation	Description
Hemangioblastomas	Commonly affect the retina, cerebellum, brainstem, and spinal cord; may cause vision changes, headaches, and ataxia.
Renal Cell Carcinoma (RCC)	Clear cell RCC is common; often bilateral and multifocal.
Pheochromocytoma	Adrenal gland tumors leading to hypertension, palpitations, sweating, and headaches.
Pancreatic Neuroendocrine Tumors	Can be functional (hormone-producing) or nonfunctional; rare but can be malignant.
Endolymphatic Sac Tumors	Benign tumors in the inner ear causing hearing loss, tinnitus, and balance problems.
Cysts	Multiple cysts may develop in the pancreas, kidneys, and epididymis (in males); usually benign.

Diagnosis

- **Genetic Testing**: Confirmation of VHL gene mutation.
- **Imaging**: MRI or CT scans to assess for characteristic tumors and cysts in the central nervous system, kidneys, adrenal glands, and pancreas.
- **Regular Screening**: Essential for early detection of tumors and includes periodic MRI of the brain, spine, abdomen, and targeted organ assessments (e.g., ophthalmologic exams for retinal hemangioblastomas).

Management

Treatment	Description
Surgical Resection	For symptomatic or high-risk hemangioblastomas, RCC, and other tumors.
Radiofrequency Ablation	Used for small renal tumors that are not amenable to surgery.
Pheochromocytoma Management	Surgical resection with preoperative alpha- and beta-blockade to control hypertension.
Endolymphatic Sac Tumor Treatment	Surgery or radiotherapy may be considered to preserve hearing and reduce symptoms.
Targeted Therapy	Newer therapies like tyrosine kinase inhibitors (e.g., sunitinib) are considered for RCC in advanced cases.

Key Points for MRCP

1. **Autosomal Dominant Inheritance**: Family history is critical in diagnosis.
2. **Multisystem Surveillance:** Essential to detect and manage tumors early.
3. **VHL Tumor Spectrum**: Hemangioblastomas, RCC, and pheochromocytomas are classic presentations.

Common licensed monoclonal antibodies

Name	Target	Licensed indication
Infliximab	TNF-α	Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis
Palivizumab	F protein on RSV	Prophylaxis, RSV in premature infants or brochopulmonary dysplasia
Abciximab	Platelet glycoprotein IIb/IIIa	High risk coronary intervention
Rituximab	CD20	Refractory low grade or follicular B cell lymphoma
Basiliximab	IL-2 receptor α chain	Prophylaxis of acute rejection in allogeneic renal transplantation
Daclizumab	IL-2 receptor α	As Basiliximab
Trastuzumab	HER 2 growth receptor	Relapsed HER2 (high) breast malignancy

IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.

Commonly Used Chemotherapy Agents

Chemotherapy Agent	Class	Mechanism of Action	Indications	Common Side Effects
Cisplatin	Platinum compound	Forms DNA crosslinks, inhibiting DNA synthesis and cell division	Solid tumors (e.g., lung, ovarian, bladder, testicular cancers)	Nephrotoxicity, ototoxicity, peripheral neuropathy, nausea/vomiting
Doxorubicin	Anthracycline	Intercalates DNA, inhibits topoisomerase II, and generates free radicals	Breast cancer, lymphomas, leukemias, sarcomas	Cardiotoxicity, myelosuppression, mucositis, alopecia

Chemotherapy Agent	Class	Mechanism of Action	Indications	Common Side Effects
Cyclo-phosphamide	Alkylating agent	Alkylates DNA, leading to DNA crosslinks and apoptosis	Breast cancer, lymphomas, multiple myeloma, solid tumors	Myelosuppression, hemorrhagic cystitis, nausea/vomiting, alopecia
Methotrexate	Antimetabolite	Inhibits dihydrofolate reductase, blocking DNA synthesis and cell division	Leukemias, lymphomas, breast cancer, rheumatoid arthritis, psoriasis	Mucositis, hepatotoxicity, myelosuppression, nephrotoxicity
5-Fluorouracil (5-FU)	Antimetabolite	Inhibits thymidylate synthase, preventing DNA synthesis	Colorectal cancer, head and neck cancers, breast cancer	Mucositis, diarrhea, hand-foot syndrome, myelosuppression
Paclitaxel	Taxane	Stabilizes microtubules, preventing cell division	Breast cancer, ovarian cancer, lung cancer	Peripheral neuropathy, myelosuppression, alopecia, hypersensitivity
Vincristine	Vinca alkaloid	Binds tubulin, inhibiting microtubule formation and disrupting cell division	Leukemias, lymphomas, multiple myeloma	Peripheral neuropathy, constipation, myelosuppression
Irinotecan	Topoisomerase I inhibitor	Inhibits topoisomerase I, causing DNA damage during replication	Colorectal cancer, pancreatic cancer	Diarrhea (acute and delayed), myelosuppression, nausea/vomiting
Bleomycin	Antitumor antibiotic	Induces DNA strand breaks through free radical formation	Testicular cancer, Hodgkin's lymphoma	Pulmonary toxicity (fibrosis), skin changes, fever, mucositis
Imatinib	Tyrosine kinase inhibitor	Inhibits BCR-ABL tyrosine kinase, blocking the proliferation of cancer cells	Chronic myeloid leukemia (CML), gastrointestinal stromal tumors (GIST)	Edema, muscle cramps, nausea, rash, myelosuppression

Chemotherapy Agent	Class	Mechanism of Action	Indications	Common Side Effects
Rituximab	Monoclonal antibody	Targets CD20 on B-cells, inducing immune-mediated cell death	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), RA	Infusion reactions, infections, myelosuppression
Trastuzumab	Monoclonal antibody	Binds to HER2 receptors, inhibiting cell growth and inducing apoptosis	HER2-positive breast and gastric cancers	Cardiotoxicity, infusion reactions, pulmonary toxicity
Pembrolizumab	Immune checkpoint inhibitor	Blocks PD-1 receptor, enhancing T-cell immune response against tumors	Melanoma, non-small cell lung cancer, head and neck cancers	Immune-related adverse events (colitis, pneumonitis, hepatitis)

Granulocyte Colony-Stimulating Factor (G-CSF)

Category	Details
Agents	- **Filgrastim**: Short-acting G-CSF - **Pegfilgrastim**: Long-acting, pegylated form of G-CSF
Mode of Action	Binds to G-CSF receptors on neutrophil precursors in the bone marrow, stimulating proliferation, differentiation, and activation of neutrophils.
Administration	- **Filgrastim**: 5–10 mcg/kg per day via subcutaneous (SC) or intravenous (IV) injection, typically administered daily until the desired neutrophil count is achieved or post-chemotherapy neutrophil nadir is resolved. - **Pegfilgrastim**: 6 mg as a single SC injection per chemotherapy cycle (longer duration due to pegylation). Only one dose per cycle is recommended due to its extended half-life.
Indications	- **Chemotherapy-Induced Neutropenia**: To reduce infection risk. - **Stem Cell Mobilization**: To collect hematopoietic stem cells for transplantation. - **Chronic Neutropenia**: In patients with severe congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. - **Myelodysplastic Syndromes (MDS)**: For selected patients with neutropenia-related infections.
Side Effects	- **Common**: Bone pain (especially lower back, pelvis), headache, fatigue. - **Rare**: Splenic rupture, acute respiratory distress syndrome (ARDS), allergic reactions. - **Long-Term Use**: Increases risk of hematologic malignancies in congenital neutropenia.

Category	Details
Special Notes	- **Avoid Administration Within 24 Hours of Chemotherapy**: To prevent severe myelosuppression. - **Monitor CBC Regularly**: Especially in patients on prolonged therapy. - **Use Pegfilgrastim Once Per Chemotherapy Cycle**: Due to its extended half-life. - **Splenic Rupture**: Watch for left upper quadrant or shoulder pain, which may indicate splenic complications.

Palliative Care

Pain Management in Palliative Care

Medication	Dose and Route	Notes
Morphine (Opioid)	2.5–5 mg orally or subcutaneously every 4 hours as needed; titrate based on response.	Suitable for moderate to severe pain; use long-acting formulations for chronic pain.
Fentanyl (Opioid)	12.5–25 mcg/hour transdermal patch, replaced every 72 hours.	Ideal for stable, chronic pain; avoid in opioid-naïve patients.
Gabapentin (Neuropathic)	Start at 100–300 mg orally at night; increase to 300 mg three times daily as tolerated.	Effective for neuropathic pain, especially in combination with opioids.
Amitriptyline (Adjuvant)	10–25 mg orally at night; increase as needed up to 75 mg.	Useful for neuropathic pain; caution in elderly due to anticholinergic effects.

Nausea and Vomiting Management in Palliative Care

Medication	Dose and Route	Notes
Ondansetron (5-HT3 Antagonist)	4–8 mg orally or IV every 8 hours.	First-line for chemotherapy- or opioid-induced nausea.
Metoclopramide (Prokinetic)	10 mg orally or subcutaneously every 6 hours.	Ideal for nausea due to gastric stasis; avoid in bowel obstruction.
Haloperidol (Dopamine Antagonist)	0.5–1 mg orally or subcutaneously every 8 hours as needed.	Effective for opioid-induced nausea and in patients with delirium.

Hiccups Management in Palliative Care

Medication	Dose and Route	Notes
Chlorpromazine	25–50 mg orally or IV every 6–8 hours as needed.	First-line for persistent hiccups.
Baclofen (Muscle Relaxant)	5 mg orally three times daily; titrate up to 20 mg three times daily as tolerated.	Effective for intractable hiccups not responsive to chlorpromazine.

Constipation Management in Palliative Care

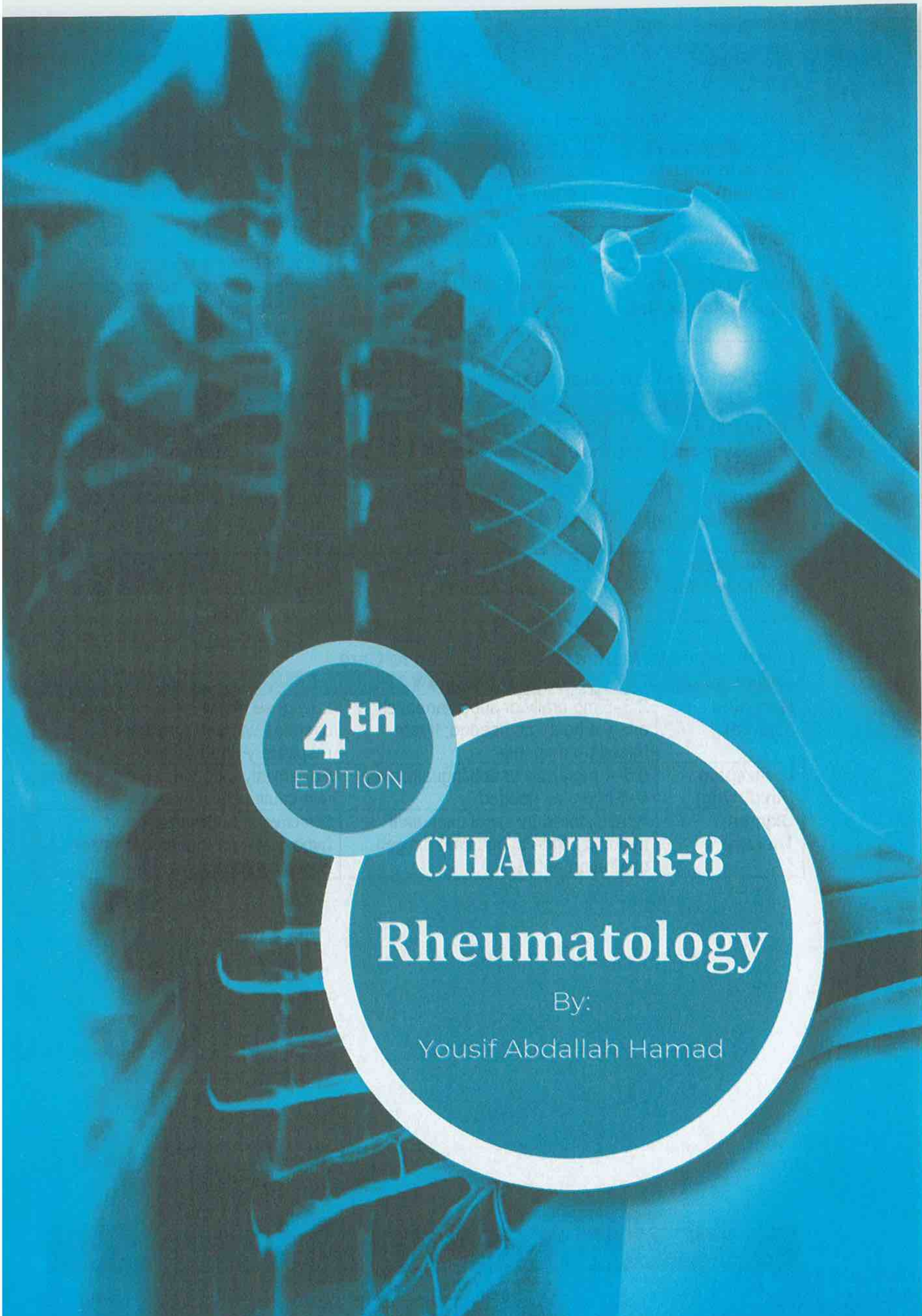
Medication	Dose and Route	Notes
Senna (Stimulant Laxative)	2–4 tablets (8.6 mg/tab) orally at night.	First-line for opioid-induced constipation; adjust based on response.
Polyethylene Glycol (Osmotic)	17 grams orally in water once daily.	Safe for daily use to maintain regular bowel movements.
Methylnaltrexone (Opioid Antagonist)	8–12 mg subcutaneously every 48 hours if other laxatives fail.	For refractory opioid-induced constipation; contraindicated in bowel obstruction.

Agitation and Confusion Management in Palliative Care

Medication	Dose and Route	Notes
Haloperidol (Antipsychotic)	0.5–2 mg orally or subcutaneously every 4–6 hours as needed.	Effective for agitation and delirium; monitor for extrapyramidal side effects.
Midazolam (Benzodiazepine)	2.5–5 mg subcutaneously every 4 hours as needed.	Rapid-acting sedative for acute agitation; useful in terminal restlessness.
Risperidone (Antipsychotic)	0.5–1 mg orally twice daily; increase as needed.	For mild-to-moderate agitation; fewer sedative effects than other antipsychotics.

Breathlessness Management in Palliative Care

Medication	Dose and Route	Notes
Morphine (Opioid)	2.5–5 mg orally or subcutaneously every 4 hours as needed; titrate based on response.	Low-dose morphine can reduce dyspnea without significant respiratory depression.
Lorazepam (Anxiolytic)	0.5–1 mg orally or sublingually every 4–6 hours as needed.	For anxiety-induced breathlessness; use cautiously in elderly.
Oxygen Therapy	Administered by nasal cannula if hypoxic; titrate to maintain oxygen saturation >90%.	Effective only if the patient is hypoxic; avoid routine use in non-hypoxic patients.



4th EDITION

CHAPTER-8
Rheumatology

By:

Yousif Abdallah Hamad

Bone Remodelling, Osteoclasts, Osteoblasts, and Bone Markers

Bone Remodelling
- Bone remodelling is a continuous process involving bone resorption by osteoclasts and bone formation by osteoblasts.
- This cycle maintains skeletal integrity and mineral homeostasis.

Osteoclasts
- Large, multinucleated cells responsible for bone resorption.
- Degrade bone matrix by secreting acids and proteolytic enzymes, releasing minerals such as calcium into the bloodstream.

Osteoblasts
- Mononucleated bone-forming cells that synthesize and secrete osteoid, primarily composed of type I collagen.
- Osteoid mineralizes to become bone.
- Produce hormones and cytokines that regulate bone metabolism.

Bone Markers
- **Markers of Bone Formation:**
  - **Bone-specific Alkaline Phosphatase (BSAP):** Indicates osteoblast activity; elevated levels reflect increased bone formation.
  - **Osteocalcin:** A non-collagenous protein secreted by osteoblasts; serves as a marker for bone formation.
  - **Procollagen Type 1 N-terminal Propeptide (P1NP):** A precursor in collagen synthesis; serum levels reflect osteoblastic activity.
- **Markers of Bone Resorption:**
  - **C-terminal Telopeptide of Type I Collagen (CTX):** A degradation product of bone collagen; elevated levels indicate increased bone resorption.
  - **N-terminal Telopeptide of Type I Collagen (NTX):** Another collagen breakdown product; used to assess bone resorption rates.
  - **Tartrate-resistant Acid Phosphatase (TRAP):** An enzyme produced by osteoclasts during bone resorption.
- **Uses of Bone Markers:**
  - **Diagnosis:** Assist in diagnosing metabolic bone diseases by indicating alterations in bone turnover.
  - **Monitoring Therapy:** Evaluate the efficacy of treatments for conditions like osteoporosis by tracking changes in bone turnover.
  - **Fracture Risk Assessment:** High levels of resorption markers may correlate with increased fracture risk.
- **Associated Diseases:**
  - **Osteoporosis:** Characterised by increased bone resorption relative to formation; markers like CTX and P1NP are used to monitor treatment response.
  - **Paget's Disease of Bone:** Elevated BSAP levels reflect increased bone formation activity.
  - **Bone Metastases:** Elevated bone resorption markers can indicate metastatic bone disease.
  - **Hyperparathyroidism:** Increased bone turnover markers due to enhanced osteoclastic activity.

Classification of Bone Markers

Markers of Bone Formation (Serum)	Markers of Bone Resorption (Serum/Urine)
Bone-derived alkaline phosphatase (ALP)	Telopeptides
Osteocalcin	Pyridinium cross-linking molecules
Procollagen type 1 propeptides	Tartrate-resistant acid phosphatase (TRAP)
	Hydroxyproline

Rheumatoid Factor (RF)

Overview

- RF is a circulating antibody (usually IgM) that reacts with the Fc portion of IgG.
- RF may belong to IgM, IgG, or IgA immunoglobulin classes.
- Conventional agglutination tests detect only IgM RF.
- High RF titres correlate with severe, progressive disease but do not reflect disease activity.

Clinical Associations

Positive RF is linked to:

- Severe erosive disease.
- Extra-articular manifestations, such as subcutaneous nodules.
- Increased mortality.

Conditions Associated with Positive RF

Condition	Percentage Positive
Sjögren's syndrome	~100%
Felty's syndrome	~100%
Mixed cryoglobulinaemia (types II & III)	40–100%
Rheumatoid arthritis	70–80%
Mixed connective tissue disease	50–60%
Infective endocarditis	~50%
Systemic lupus erythematosus (SLE)	20–30%
Systemic sclerosis	~30%
Polymyositis/Dermatomyositis	5–10%
General population	~5%

Rheumatoid factor is an IgM antibody against IgG

Rheumatoid arthritis (RA)

Definition

- an idiopathic inflammatory autoimmune disorder of unknown aetiology, that primarily affects the joints (e.g., causes pain, swelling, synovial destruction, deformities), but may also manifest with extraarticular features (e.g., rheumatoid nodules, pulmonary fibrosis).

Epidemiology: **Prevalence = 1%.** F: M ratio = 3:1. Peak onset = 30-50 years.

Risk factors

- **Genetic factors:** HLA-DR4 associated with RA (70%) and **Felty's syndrome (90%) (a triad of rheumatoid arthritis, splenomegaly and neutropenia)**
- **Environmental factors**
- **Microbial factor: Proteus mirabilis infection**

Pathophysiology

- Interstitial tissue conversion of arginine to citrulline (Citrullinated proteins) → recognised as foreign by CD4+ T → (**autoimmune inflammation**) Production of autoantibodies (Anti-cyclic citrullinated peptide (anti-CCP) antibody and Rheumatoid factor (RF) **PLUS** secretion of inflammatory mediators (TNF-α, IL-1, IL-6) in the synovium → destruction of articular cartilage

Diagnosis

- **The diagnosis is clinical.** NICE has stated that clinical diagnosis is more important than criteria (e.g., American College of Rheumatology criteria). Consider RA in patients with **arthralgia, joint stiffness,** and **synovitis** lasting ≥ 6 weeks
- American College of Rheumatology criteria score 6/10

American College of Rheumatology criteria (2010)

A. Joint involvement	Score
1 large joint	0
2 - 10 large joints	1
1 - 3 small joints	2
4 - 10 small joints	3
10 joints (at least 1 small joint)	5

B. Serology	Score
Negative RF and Anti-CCP	0
Low-positive RF or Anti-CCP	2
High-positive RF or Anti-CCP	3

C. Acute-phase reactants	Score
Normal CRP and ESR	0
Abnormal CRP or ESR	1

D. Duration of symptoms	Score
< 6 weeks	0
> 6 weeks	1

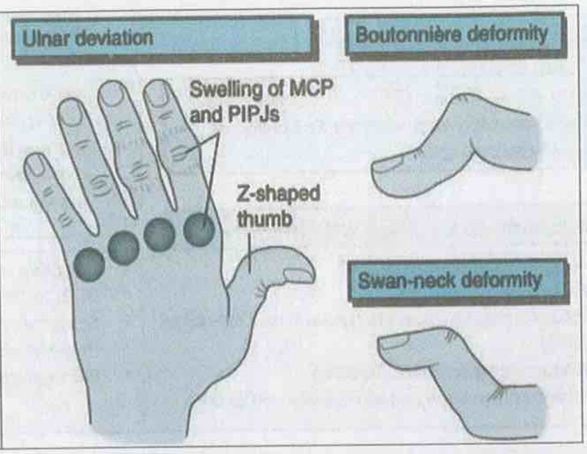
A score of 6/10 is needed for definite rheumatoid arthritis

Features

Articular manifestations	Extra-articular manifestations
Polyarthralgia: Symmetrical pain and swelling of affected joints ▪ **Frequently affected joints:** Metacarpophalangeal (MCP), Proximal interphalangeal (PIP), wrist joints ▪ Metatarsophalangeal joints (the earliest manifestation of RA in the feet) ▪ **C1 and C2 articulations** (atlantoaxial subluxation: a loss of ligamentous stability between the atlas (C1) and axis (C2), which can result in compression of the spinal cord, medulla, and/or vertebral arteries by the odontoid process, especially upon neck flexion. Most commonly caused by Down syndrome, rheumatoid arthritis, and trauma). ▪ **Spared joints** (not typically affected): Distal interphalangeal (DIP) joints, sacroiliac and vertebral joints, except for the C1 and C2 articulations. **Morning stiffness** > 30 min, improves with activity **Joint deformities**	**Constitutional symptoms:** Low-grade fever, myalgia, weight loss **Rheumatoid nodules:** Commonly in areas pressure area (e.g., extensor side of the forearm, bony prominences) **Lungs:** ▪ **Cricoarytenoid arthritis** (75%) → stridor (worsen post-operative). The best diagnostic test → Spirometry with flow–volume loop. May need urgent tracheostomy and steroids. ▪ **Pleuritis & pleural effusion** ▪ **Interstitial lung disease** (e.g., organizing pneumonia) ▪ Caplan syndrome (rheumatoid pulmonary nodules + fibrosis + pneumoconiosis). ▪ **Eye:** ▪ **Keratoconjunctivitis sicca** (dry eyes) (most common) ▪ **Scleritis, and episcleritis** **Hematological:** ▪ **Anemia** (Normocytic of chronic disease. Microcytic iron deficiency due to NSAIDs-related GI bleed. Macrocytic due to Methotrexate-related folate deficiency) ▪ **Neutropenia** ▪ **Splenomegaly** **Heart:** constrictive pericarditis **Musculoskeletal:** Tenosynovitis and bursitis, Carpal tunnel syndrome **Vascular:** Peripheral vasculitis: livedo reticularis, Raynaud phenomenon

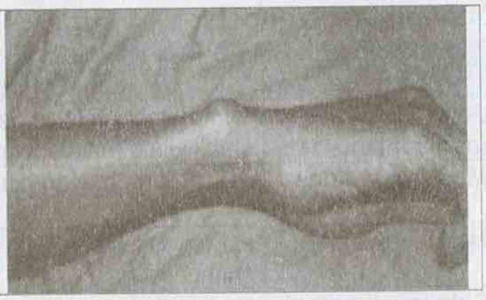
Hand Joint Deformities

- **Ulnar deviation of the fingers**
- **Z deformity of the thumb:** hyperextension of the interphalangeal joint with fixed flexion of the MCP joint
- **Boutonniere deformity:** PIP flexion and DIP hyperextension.
- **Swan neck deformity:** PIP hyperextension and DIP flexion



Piano key sign

When the ulnar head is depressed, it springs back into position like a Piano key (due to dorsal subluxation of the ulna)



Investigations

- **Serological studies**
  - ⇨ **Anti-cyclic citrullinated peptide (Anti-CCP) antibodies**: sensitivity of 70-80% & **more specific (90-95%).** It is also a prognostic marker.
  - ⇨ Rheumatoid factor (RF): Present in 70–80% of patients, but not specific to RA
  - ⇨ **Up to 30% of patients with RA are negative for Anti-CCP and RF** (i.e., seronegative RA)
- **X-ray of both hands and feet**

Early x-ray findings	Late x-ray findings
• Loss of joint space • **Juxta-articular osteoporosis** • Soft-tissue swelling	• Periarticular erosions • Subluxation

- **Analysis of synovial fluid:** Sterile specimen with leukocytosis (WBC count 5000–50,000/mcL), ↑**neutrophils** & protein levels.

The radiographic features of rheumatoid arthritis can be remembered by the mnemonic LESS: Loss of joint space, Erosions, Soft tissue swelling, and Soft bones (osteopenia)

Poorly controlled rheumatoid arthritis + proteinuria and hypoalbuminaemia raises the possibility of systemic amyloidosis → Rectal biopsy

Rheumatoid factor (RF)

Rheumatoid factor (RF): a circulating IgM antibody which reacts with the Fc portion of the patients own IgG.

Indicators of positive RF in RA

- More severe erosive disease (but NOT a marker of disease activity).
- Extra-articular manifestations including subcutaneous nodules
- Increased mortality.

Conditions associated with positive RF

- Sjogren's syndrome (100%)
- Felty's syndrome (100%)
- Mixed cryoglobulinemia (types II and III) - 40 to 100%
- Rheumatoid arthritis (70-80%)
- Mixed connective tissue disease - 50 to 60%
- Infective endocarditis (50%)
- SLE (20-30%)
- Systemic sclerosis (30%)
- Polymyositis/dermatomyositis - 5 to 10%
- General population (5%)

Differential diagnosis

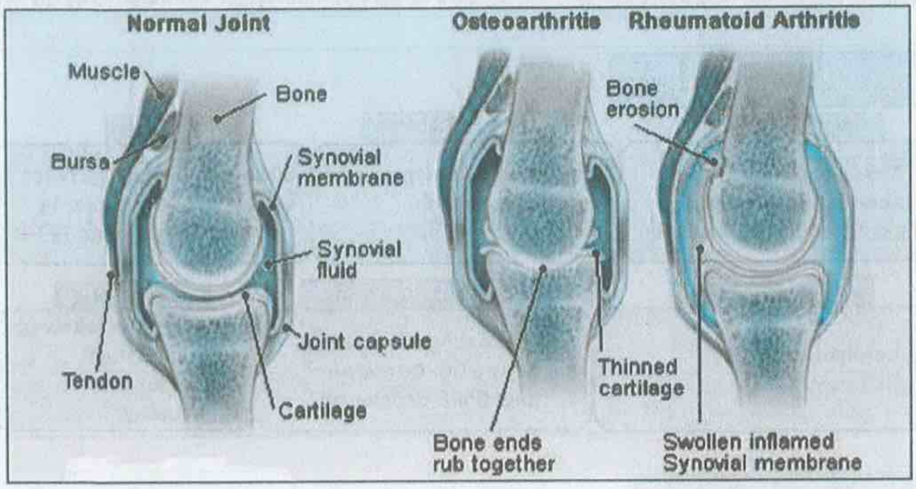
Rheumatoid arthritis VS Psoriatic arthritis

Feature	Rheumatoid Arthritis (RA)	Psoriatic Arthritis (PsA)
Joint involvement	Symmetrical involvement of small joints (hands, wrists).	Asymmetrical joint involvement, often large joints (knees, ankles).
Morning stiffness	Lasts more than an hour.	Typically shorter duration, less than 30 minutes.
Nail involvement	Rarely associated with nail changes.	Nail pitting, onycholysis, and other nail deformities are common.
Skin involvement	No direct skin involvement.	Associated with psoriasis (scaly, red plaques on skin).
Rheumatoid Factor (RF) and **Anti-CCP antibodies**	Often positive (seropositive RA).	Usually negative for RF (seronegative).

Rheumatoid arthritis VS Osteoarthritis

	Rheumatoid arthritis	Osteoarthritis
Pathophysiology	Autoimmune (inflammatory)	Degenerative due to ↑ wear and tear on joints → loss of cartilage (non-inflammatory)
Age of starting	At any age	Usually later in life
Speed of onset	Rapid, over weeks to months	Slow, over yeas
Pain	Improves with movement	Worse with movement and better with rest
Primary joint affected	**Proximal** interphalangeal	**Distal** interphalangeal
	Metacarpophalangeal	Carpometacarpal
Heberdens nodes	Absent	Present

	Rheumatoid arthritis	Osteoarthritis
Joint characteristics	Soft, warm and tender	Hard and bony (little or no swelling)
Stiffness	Worse after resting (morning stiffness)	If present, worse after effort, may be described as evening stiffness
	Usually > 1 hour	Usually <1 hour
Systemic symptoms	Present (eg: fatigue)	Absent
RF and anti-CCP	Positive	Negative
ESR and C-reactive protein	Elevated	Normal
X-ray	Osteophytes absent	Osteophytes may be present



Prognosis: Poor prognostic features:

- **Positive anti-CCP (the poorest prognostic factor)** or Rheumatoid factor
- HLA DR4
- Insidious onset: Acute onset is not a poor prognosis.
- Early articular erosions on X-ray (e.g. within the first 6 months)
- Extra-articular features e.g. nodules
- Female sex.

Complication

- **↑ Risk of IHD**
- **Popliteal cysts (Bakers cysts)**

Management

- **NSAIDs and glucocorticoids** (Short-term until DMARD take effect)
- **Start disease-modifying anti-rheumatic drugs (DMARDs) immediately, start monotherapy and titrate the dose, if not controlled add another DMARDs**

Disease-modifying anti-rheumatic drugs (DMARDs)

Methotrexate (MTX)

First line in moderate to high disease activity (takes 6 -12 weeks to achieve full effect)

Mode of Action

Inhibits dihydrofolate reductase enzyme, essential for the synthesis of purines and pyrimidines

Dose

7.5 mg once weekly, adjusted according to response; maximum 20 mg per week + folic acid 5 mg once weekly

Side-effects

- Myelosuppression
- Liver cirrhosis
- Pneumonitis
- Ulcerative Mucositis

Contraindications

- Pregnancy and lactation
- Chronic liver disease
- Immunodeficiency
- bone marrow suppression

Monitoring

CBC, LFT, and RFT monthly for 3 months, then every 3 months

Overdose

- Multi-organ failure
- I.V folinic acid (Calcium folinate) is the antidote

Hydroxychloroquine (HCQ)

Indications

RA in low disease activity or if MTX is contraindicated, e.g., during pregnancy. SLE & Sjögren

Mode of Action

Impairs complement-dependent antigen-antibody reactions

Dose

500 mg once daily; increase weekly by 500 mg up to 1 g twice daily, maximum 1g TID

Side-effects

- Hyperpigmentation
- Retinopathy

Contraindications

- Preexisting retinopathy)
- Severe G6PDd (safe in mild G6PD deficiency)

Monitoring

Baseline and follow-up Ophthalmologic evaluation for retinopathy

Sulfasalazine (SSZ)

In low disease activity or if MTX is contraindicated, e.g., during pregnancy.

Mode of Action

A prodrug composed of 5-aminosalicylic acid (5-ASA) linked to sulfapyridine

Dose

500 mg once daily; increase weekly by 500 mg up to 1 g twice daily, maximum 1g TID

Side-effects

- Agranulocytosis
- Skin reactions
- Hepatitis
- Haemolytic anaemia in G6PDd
- Men infertility (oligospermia)

Contraindications

- Severe renal or hepatic impairment
- Porphyria
- Severe G6PDd

Monitoring

CBC, LFT, and RFT monthly for 3 months, then every 3 months

Leflunomide (LEF)

Indications
- Rheumatoid arthritis, if MTX cannot be used
- Psoriatic arthritis
- SLE
- Dermatomyositis

Side-effects
- Diarrhea (most common
- Hepatotoxicity
- Pneumonitis
- Hypertension
- Very low risk of Leukopenia

Indications of washout
- Hepatotoxicity (if AST or ALT >3 times the upper limit of normal). If < 3 times of normal → reduce the dose to 10 mg and follow LFT.
- Hypertension (if BP remains >140/90 mmHg
- Weight loss (if >10% weight loss without other cause)
- Plan of pregnancy

Mode of Action

Inhibits dehydrogenase (DHOD) → inhibition of pyrimidine → ↓proliferation of T lymphocytes.

Contraindications
- Pregnancy & Lactation
- Preexisting liver disease.
- Preexisting interstitial lung disease

Dose

20 mg daily (has long half-life)

Monitoring

CBC, RFT, LFT monthly for 3 months, then every 3 months.

Toxicity treatment

Washout with activated charcoal and Cholestyramine 8 g 3 times daily for 11 days

- **Biologic DMARDs**
  - ⇨ **Indications:** persistent moderate or severe disease activity after 3 months of conventional DMARD therapy. Most effective when used in combination with a nonbiologic DMARD
  - ⇨ **TNF-inhibitors**
    - Etanercept: SC administration twice weekly
    - Infliximab: IV administration
    - Adalimumab: SC administration
  - ⇨ **Rituximab**
    - **Action → Anti-CD20 monoclonal antibody, results in B-cell depletion.**
    - **Prescription** →Two doses of 1g intravenous infusions are given two weeks apart.
    - **Indications (Nice guidelines) → Rituximab + methotrexate** is recommended as an option for inadequate response to or intolerance of other DMARDs, including at least one TNF-α) inhibitor.
  - ⇨ **Adverse effects & Administration:**
    - **Immunosuppression** → Infections. Live vaccines should not be given to patients on biologic agents.
    - **TB reactivation: TB screen all patients by interferon gamma release assay** (not altered by previous TB or previous BCG vaccination as Mantoux test). **If active TB**, detected should **complete two months of full treatment before starting biologic therapy. If latent TB (normal chest x-ray with positive interferon test), treat** with (either isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time as being started on anti-TNF alpha treatment.

- **Hepatitis B reactivation:** In patients with hepatitis B or C, immuno-suppressive therapy can be safely pre-scribed along with concomitant antiviral therapy.
- **Opportunistic infection with JC virus → Progressive multifocal leukoencephalopathy (PML)**
- **↑ post-operative infections and delayed wound healing → Hold biologic treatment for 2–4 weeks before surgery,** restart postoperatively if there is no evidence of infection and once wound healing is satisfactory.

Monitoring

- Check FBC, RFT & LFT at least **every 12 weeks** and **consider interruption in treatment** if any abnormality.
- **Discontinue DMARDs (except hydroxychloroquine) during acute infection.**
- Check CRP (disease activity marker) **monthly until treatment has controlled the disease** to guide treatment.

Step-1	▪ Glucocorticoids (short course) ▪ DMARDs monotherapy	▪ Methotrexate (MTX) ▪ If MTX is contraindicated or mild RA → Hydroxychloroquine (HCQ) or sulfasalazine (SSZ)
Step-2	Remain symptomatic after 3- 6 months at optimal dose → DMARDs dual or triple therapy	▪ If on HCQ or SSZ → add or switch to MTX ▪ If on MTX → add TNF inhibitor (etanercept, adalimumab, infliximab, golimumab, or certolizumab pegol)

Do not prescribe biologics for RA before a trial of methotrexate (or other conventional synthetic disease- modifying antirheumatic drugs [DMARDs])

RA in pregnancy and breast-feeding

Disease activity
- Reduction in disease activity during pregnancy.
- Increase the risk of flare in the first three months postpartum

Safe drugs
- Glucocorticoids
- Hydroxychloroquine (HCQ)
- Azathioprine (AZA)
- Sulfasalazine (SSZ)
- (TNF) inhibitors

Contraindicated drugs
- Methotrexate (MTX)
- Leflunomide (LEF)

Felty's Syndrome

Definition

- A severe subtype of rheumatoid arthritis (RA) characterised by the triad of **arthritis, splenomegaly, and neutropenia**.
- Considered an **extra-articular manifestation** of RA.

Epidemiology

- Occurs in **<1%** of patients with rheumatoid arthritis.

Risk Factors

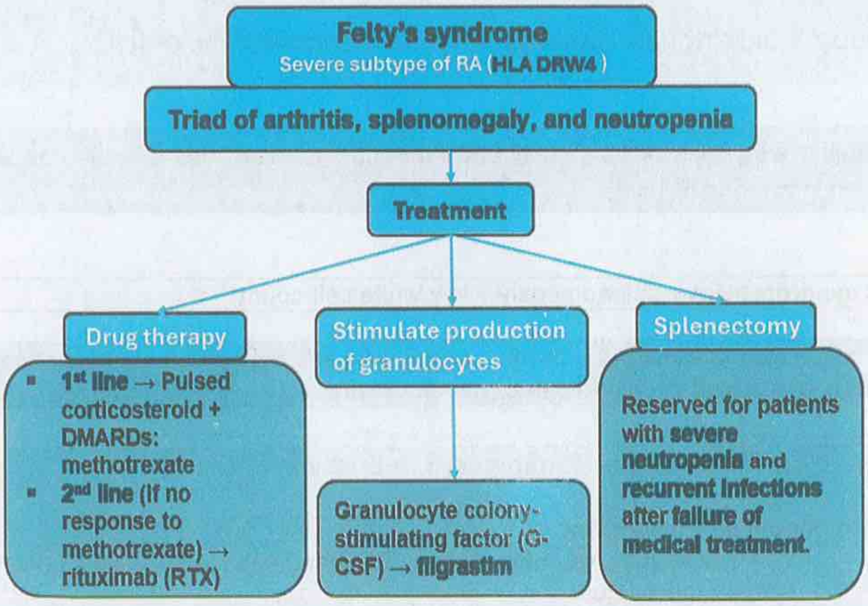
- Long-standing, **seropositive RA**.
- Associated with **HLA-DR4** in 95% of cases (compared to 70% in RA alone).

Clinical Features

- **Triad**:
  - Arthritis.
  - Splenomegaly.
  - Neutropenia (**absolute neutrophil count < 2000/μL**).
- Neutropenia increases the risk of **recurrent bacterial infections**.
- **ANA positive** in >90% of patients.

Treatment

1. **Initial**: Pulsed corticosteroid therapy.
2. **First-line**: Disease-modifying antirheumatic drugs (DMARDs), such as **methotrexate**.
3. **Second-line**: **Rituximab (RTX)** for patients unresponsive to methotrexate.
4. **Adjunctive**:
   - **Granulocyte colony-stimulating factor (G-CSF, filgrastim)** to stimulate granulocyte production.
5. **Splenectomy**:
   - Reserved for severe neutropenia and recurrent infections refractory to medical therapy.



Rheumatoid arthritis - TNF is key in pathophysiology

- **Around 70% of patients with rheumatoid arthritis are HLA-DR4.**
- **atients with Felty's syndrome (a triad of rheumatoid arthritis, splenomegaly and neutropaenia) are even more strongly associated with 90% being HLA-DR4**

Rheumatoid arthritis - TNF is key in pathophysiology

The earliest manifestation of rheumatoid arthritis in the feet → swelling of the metatarsophalangeal joints

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

The radiographic features of rheumatoid arthritis can be remembered by the mnemonic LESS: Loss of joint space, Erosions, Soft tissue swelling, and Soft bones (osteopenia)

Early x-ray findings	Late x-ray findings
• loss of joint space • **juxta-articular osteoporosis** • soft-tissue swelling	• periarticular erosions • subluxation

Proteus mirabilis infection has been hypothesised to contribute to the development of rheumatoid arthritis (RA) in genetically predisposed individuals.

Rheumatoid arthritis: patients have an increased risk of IHD

Popliteal cysts ('Baker's cysts') may occur in rheumatoid arthritis following persistent effusion into the knee joint.

Felty's syndrome (RA + splenomegaly + low white cell count)

Poorly controlled rheumatoid arthritis + proteinuria and hypoalbuminaemia raises the possibility of systemic amyloidosis → Rectal biopsy

Guidance on TNF-Blocker Management in Surgical Patients

- **Preoperative Management**:
  - Withhold **etanercept**, **infliximab**, and **adalimumab** for **2–4 weeks** prior to major surgical procedures.

- This minimises the risk of postoperative infections and allows for normal inflammatory responses critical for wound healing.

- **Postoperative Management**:
  - Restart therapy **postoperatively** only if:
    - There is **no evidence of infection**.
    - Wound healing is deemed **satisfactory** by the surgical team.

The first-line treatment for newly diagnosed active RA → combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as soon as possible, ideally within 3 months of the onset of persistent symptoms.

RA during pregnancy → continue current dose of azathioprine and add folic acid

Seronegative spondyloarthropathies

Definition

- A group of inflammatory rheumatic diseases characterised by:
  - **Seronegativity**: Absence of rheumatoid factor (RF) and anti-CCP antibodies.
  - **Axial and peripheral arthritis**, enthesitis, and dactylitis.
  - Strong association with **HLA-B27**.

Types

1. **Ankylosing Spondylitis (AS)**:
   - Chronic inflammatory disease primarily affecting the axial skeleton (spine and sacroiliac joints).
   - Associated with progressive spinal stiffness and fusion.
2. **Psoriatic Arthritis (PsA)**:
   - Inflammatory arthritis occurring in patients with psoriasis.
   - Can involve peripheral joints, axial skeleton, and entheses.
3. **Reactive Arthritis**:
   - Arthritis developing after gastrointestinal or genitourinary infections (e.g., Salmonella, Shigella, Chlamydia).
   - Classic triad: arthritis, urethritis, and conjunctivitis.
4. **Enteropathic Arthritis**:
   - Arthritis associated with inflammatory bowel disease (IBD) such as Crohn's disease or ulcerative colitis.
   - Can involve axial or peripheral joints.
5. **Undifferentiated Spondyloarthropathy**:
   - Inflammatory arthritis not fitting criteria for specific subtypes.

Clinical Features

- **Articular Manifestations**:
  - Axial involvement: sacroiliitis and spondylitis.
  - Peripheral arthritis: typically asymmetric, oligoarticular.
  - Enthesitis: inflammation at tendon/ligament insertion sites (e.g., Achilles tendon).
  - Dactylitis: "sausage digits."

- **Extra-Articular Manifestations**:
  - Uveitis (common in AS).
  - Psoriasis (PsA).
  - IBD symptoms (enteropathic arthritis).
  - Mucocutaneous lesions (reactive arthritis).

Diagnosis

- **Clinical evaluation and imaging:**
  - **X-rays**: Sacroiliitis or syndesmophytes (AS).
  - **MRI**: Early detection of inflammation.
- **Laboratory**:
  - Negative RF and anti-CCP.
  - Positive **HLA-B27** in many cases.

Treatment

1. **Non-Pharmacological**:
   - Physiotherapy and exercise to maintain mobility.
   - Patient education and lifestyle modifications.
2. **Pharmacological**:
   - **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**: First-line treatment for pain and inflammation.
   - **Disease-Modifying Anti-Rheumatic Drugs (DMARDs)**:
     - Conventional DMARDs (e.g., sulfasalazine) for peripheral arthritis.
     - Biologic DMARDs (e.g., TNF inhibitors like etanercept, adalimumab) for axial disease.
   - **Corticosteroids**: Local injections for enthesitis or dactylitis.
   - **Secukinumab** or **Ixekizumab**: IL-17 inhibitors for refractory cases.
3. **Surgical**:
   - Rarely required but may involve joint replacement for severe damage.

Key Points

- **Seronegative**: No RF or anti-CCP antibodies.
- Strongly linked to **HLA-B27**.

Mixed connective tissue disease (MCTD)

Definition: an overlap syndrome characterised by combinations of clinical features of SLE, systemic scleroderma, RA and polymyositis **(e.g. arthralgia, myositis and Raynaud's)**.

Diagnosis:

1) **Anti-U1 RNP antibodies; and**
2) **At least three of the following features**:
   - ⇨ Digital swelling
   - ⇨ Raynaud phenomenon
   - ⇨ Synovitis
   - ⇨ Myositis
   - ⇨ Acrosclerosis (stiffness of the skin)

Treatment: directed at the specific disease manifestations, similar to SLE, SSc, and other rheumatic diseases

Prognosis: Most deaths are due to heart failure caused by pulmonary arterial hypertension.

Comparison of MCTD vs Overlap Syndrome

Aspect	MCTD	Overlap Syndrome
Definition	A distinct autoimmune disorder with features of systemic lupus erythematosus (SLE), systemic sclerosis, and polymyositis, characterized by high anti-U1 ribonucleoprotein (RNP) antibodies.	Presence of features from two or more well-defined autoimmune diseases (e.g., SLE, systemic sclerosis, rheumatoid arthritis) without exclusive criteria for one.
Primary Features	Specific overlapping features of SLE, systemic sclerosis, and polymyositis.	Varies widely; can involve any combination of systemic autoimmune diseases such as lupus with myositis or rheumatoid arthritis with systemic sclerosis.
Key Diagnostic Marker	Anti-U1 RNP antibodies (high titres).	No specific antibody; depends on the overlap of specific diseases (e.g., ANA, anti-dsDNA for lupus; anti-CCP for RA).
Prevalence	Less common; considered a distinct clinical entity.	More common, often seen as coexistence of known autoimmune disorders.
Pulmonary Involvement	Often associated with interstitial lung disease and pulmonary hypertension.	Can occur, but depends on the overlapping diseases involved.
Management Approach	Tailored to treat the most active component (e.g., corticosteroids for myositis, hydroxychloroquine for lupus-like features).	Managed based on the dominant overlapping condition(s) (e.g., immunosuppressants for lupus, DMARDs for RA).

Ankylosing spondylitis

Definition:

A seronegative spondyloarthropathy, characterized by chronic inflammation of the spine and sacroiliac joints.

Pathophysiology:

- Autoimmune disorder with 90-95% HLA-B27 positive patients.
- Polygenic inheritance.

Epidemiology:

- Predominantly affects males (3:1 ratio).
- Commonly presents between 20-40 years of age.

Features:

- **Articular manifestations:**
  - **Inflammatory back pain:** Morning stiffness > 30 minutes, improving with activity.
  - **Tender sacroiliac joints:** Positive Mennell's sign.
  - Reduced spinal mobility, positive Schober's test, loss of lumbar lordosis, thoracic kyphosis.
  - Enthesitis, dactylitis, and peripheral arthritis (in 25% of cases, more common in females).

- **Extra-articular manifestations:**
  - **Anterior uveitis:** The most common extra-articular feature (40% prevalence).
  - **Pulmonary involvement:** Restrictive defect with reduced chest expansion.
  - **Cardiac:** Aortic valve insufficiency and conduction abnormalities.
  - **Gastrointestinal:** Symptoms of inflammatory bowel disease (e.g., diarrhea with blood).
  - **Renal:** Association with IgA nephropathy.

Investigations:

- **Blood tests:** Raised inflammatory markers (CRP, ESR); autoantibodies (e.g., ANA, rheumatoid factor) are negative.
- **HLA-B27 testing:** Positive in 90% of cases, but not diagnostic on its own.
- **X-ray:** Sacroiliitis, squaring of vertebrae, "bamboo spine," syndesmophytes, and apical lung fibrosis.
- **MRI:** More sensitive in early detection (bone marrow edema and joint erosions).
- **Spirometry:** May show a restrictive defect.

Diagnostic Criteria: (Modified New York Criteria)

- **Clinical:**
  - Chronic low back pain > 3 months, improving with exercise but not relieved by rest.
  - Limited spine motion in sagittal and frontal planes.
  - Reduced chest expansion.
- **Radiological:**
  - Sacroiliitis on imaging.
- **Diagnosis:**
  - Definite ankylosing spondylitis if both radiological and at least one clinical criterion are met.

Management:

- **Non-pharmacological:** Regular exercise (e.g., swimming) and physiotherapy.
- **Pharmacological:**
  - **First-line:** NSAIDs.
  - **Second-line:** TNF-α inhibitors (e.g., etanercept, adalimumab).

Ankylosing spondylitis: Diagnostic criteria

- **Lower back pain for > 3 months in patients < 45 years of age and one of the following:**
  - **Sacroiliitis confirmed on x-ray or MRI and ≥ 1 typical clinical or laboratory finding**
  - **A positive HLA-B27 test and ≥ 2 typical clinical or laboratory findings**

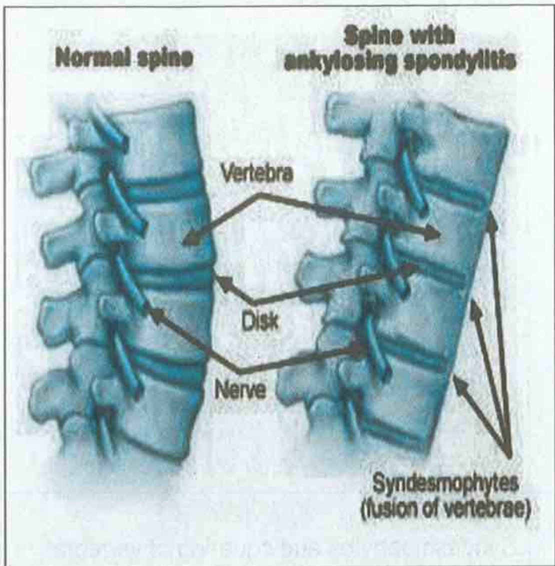
40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints	Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

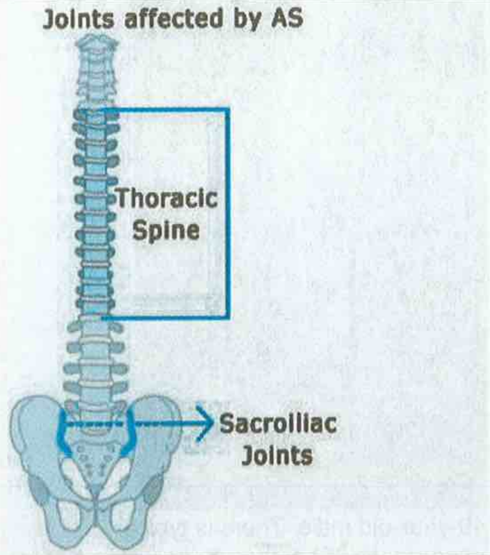
Typically a young man who presents with lower back pain and stiffness of insidious onset

Ankylosing spondylitis features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis

Ankylosing spondylitis - x-ray findings: subchondral erosions, sclerosis
and squaring of lumbar vertebrae





Syndesmophytes grow vertically, as opposed to osteophytes, which grow horizontally

the best option to confirm a diagnosis of ankylosing spondylitis → Sacroiliac joints x ray

Syndesmophytes vs. osteophytes		
	Syndesmophytes	**Osteophytes**
Definition	• Ossification or calcification of the annulus fibrosus or a spinal ligament	• Lipping of vertebral bodies
Radiographic features	• Symmetrical, vertical growth, directly from vertebral body to vertebral body • Full manifestation: "bamboo spine"	• **Horizontal growth**
Etiology	• Inflammatory spine disease (e.g., AS)	• Degenerative spine disease (e.g., diffuse idiopathic skeletal hyperostosis)

Avascular necrosis (AVN)

Definition

- death of bone tissue due to interruption of blood supply; most commonly affects the epiphysis of long bones such as the femur.

Causes

- **long-term steroid use**
- **sickle cell disease**, Gaucher disease
- Cellular toxicity (e.g., **chemotherapy**, radiotherapy, alcohol excess)
- trauma

Features

- initially asymptomatic
- pain in the affected joint

Investigation

- plain x-ray findings may be normal initially
- **MRI is the investigation of choice.** It is more sensitive than radionuclide bone scanning

Treatment

- Joint replacement (e.g., hip, shoulder, knee)

Behcet's syndrome

Definition:

- Behçet's syndrome (Behçet's disease) is a chronic, multisystem inflammatory disorder characterized by recurrent oral and genital ulcers, skin lesions, and uveitis. It is classified as a type of vasculitis that affects both small and large blood vessels.

Pathophysiology:

- Abnormal immune response triggered by environmental factors (e.g., infections) in genetically predisposed individuals.
- HLA-B51 is the genetic marker most associated with Behçet's disease.

Epidemiology:

- Most common in countries along the ancient Silk Road (e.g., Turkey, Middle East, and Asia).
- Typically affects individuals aged 20-40 years.
- More severe manifestations are seen in men compared to women.

Features:

- **Oral ulcers:** Painful, recurrent aphthous ulcers; often the first symptom.
- **Genital ulcers:** Painful, recurrent, similar to oral ulcers, may scar upon healing.
- **Skin lesions:** Erythema nodosum-like lesions, pustules, acneiform eruptions.
- **Ocular involvement:** Uveitis (anterior or posterior), retinal vasculitis, potentially leading to blindness.
- **Joint involvement:** Non-erosive arthritis (commonly affects knees, ankles, and wrists).
- **Neurological:** Meningoencephalitis, cranial nerve palsies, seizures (neuro-Behçet's).
- **Vascular:** Thrombosis, arterial aneurysms, vasculitis (risk of deep vein thrombosis or pulmonary embolism).
- **Gastrointestinal:** Ulcers in the ileocecal region, mimicking inflammatory bowel disease.

Diagnosis:

- **Clinical diagnosis:** Based on recurrent oral and genital ulcers along with other systemic manifestations.
- **Pathergy test:** Skin hypersensitivity reaction to minor trauma (intradermal needle prick).
- **Imaging:** MRI to assess CNS involvement; Doppler ultrasound for vascular complications.
- **Laboratory tests:** Nonspecific findings such as elevated ESR, CRP; no specific diagnostic marker.

Complications:

- Vision loss due to uveitis.
- Vascular complications, including thromboembolism.
- CNS involvement leading to neurological deficits or seizures.
- GI bleeding and perforation.

Management:

- **Topical therapy:**
  - Oral and genital ulcers: Topical corticosteroids or sucralfate.
- **Systemic therapy:**
  - **Colchicine:** Used for arthritis and skin lesions.
  - **Corticosteroids:** To control severe inflammation in acute flares.
  - **Immunosuppressants:** Azathioprine, cyclosporine, or methotrexate for severe ocular or CNS involvement.
  - **Biologics:** TNF-α inhibitors (e.g., infliximab, adalimumab) for refractory cases.
- **Anticoagulation:** In cases with thrombosis.

Behcet's syndrome: The classic triad of symptoms are:

1. **Oral ulcers**
2. **Genital ulcers**
3. **Anterior uveitis (iritis)**

Behcet's syndrome → PATHERGY

Positive pathergy test, Aphthous mouth ulcers, Thrombosis (arterial and venous), Hemoptysis (pulmonary artery aneurysm), Eye lesions (uveitis, retinal vasculitis), Recurrent Genital ulcers, Young at presentation (3rd decade)

Chronic fatigue syndrome (CFS) (myalgic encephalomyelitis)

Category	Details
Definition	Chronic Fatigue Syndrome (CFS) or Myalgic Encephalomyelitis (ME) is a complex, debilitating disorder characterised by profound fatigue not relieved by rest and worsened by physical or mental activity.
Causes	The exact cause is unknown; potential triggers include viral infections, immune dysfunction, hormonal imbalance, and psychological stress.
Epidemiology	Affects both adults and children, **more common in women**. Onset is typically between 20-50 years of age.
Pathophysiology	Thought to involve immune dysfunction, altered energy metabolism, autonomic nervous system dysregulation, and possibly infections or inflammation.
Symptoms	**- Persistent fatigue lasting ≥6 months not alleviated by rest** - NICE guidelines recommend suspecting myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in persistent fatigue for **6 weeks** or more, significantly impairing their ability to engage in usual daily activities, and not explained by another illness. - Post-exertional malaise (worsening of symptoms after activity) - Sleep disturbances - Cognitive difficulties (brain fog) - Joint and muscle pain (myalgia) **- Painful lymph nodes without enlargement** - Sore throat, swollen lymph nodes - Headaches - Dizziness and orthostatic intolerance
Diagnostic Criteria	- Diagnosed after at least **6 months** of **disabling fatigue affecting mental and physical function more than 50% of the time** in the **absence of other disease** which may explain symptoms. - The NICE (UK) guidelines recommend ruling out other conditions causing fatigue, such as hypothyroidism or anaemia.
Investigations	- Full blood count (FBC), thyroid function tests, and other relevant investigations to rule out alternative diagnoses - No specific diagnostic biomarker for CFS/ME
Management	- **Pacing:** Self-management strategy to avoid overexertion and manage energy - **Cognitive Behavioural Therapy (CBT):** Helps address the psychological impact - **Graded Exercise Therapy (GET):** Controversial; should only be considered carefully, as it can worsen symptoms in some cases - **Medications:** Symptomatic treatment (e.g., pain relief, sleep aids, antidepressants)
Complications	- Social isolation, depression, and anxiety - Reduced quality of life - Inability to work or perform daily activities
Prognosis	- Symptoms may persist for months or years; relapses are common. - Some patients improve over time, but complete recovery is rare.
Differential Diagnosis	- Hypothyroidism - Sleep disorders (e.g., obstructive sleep apnoea) - Depression and anxiety - Autoimmune diseases (e.g., lupus)

Chronic fatigue syndrome (also known as myalgic encephalomyelitis) → unexplained, persistent, and relapsing fatigue.

Complex Regional Pain Syndrome (CRPS) vs Compartment Syndrome

Category	Complex Regional Pain Syndrome (CRPS)	Compartment Syndrome
Definition	Chronic pain condition, typically affecting a limb after injury or trauma, characterized by pain disproportionate to the initial injury.	Condition caused by increased pressure within a closed muscle compartment, impairing blood flow and nerve function.
Cause	- Injury, surgery, or trauma (e.g., fracture) - Nerve injury or malfunction	- Trauma (e.g., fractures) - Tight casts/bandages - Crush injuries or burns
Pathophysiology	Abnormal response of the peripheral and central nervous systems, causing heightened pain perception and autonomic dysfunction.	Increased pressure within a compartment leads to reduced perfusion, tissue ischemia, and nerve damage.
Symptoms	- Severe, burning pain - Swelling, redness - Allodynia (pain from non-painful stimuli) - Temperature or colour changes in the limb - Limited range of motion	- Severe, unrelenting pain not relieved by rest - Pain worsens with passive stretch - Swelling, tightness - Numbness, tingling, or paralysis (late stages)
Onset	Gradual or delayed onset after trauma or injury (weeks to months)	Acute onset, usually within hours of trauma or injury
Investigations	- Clinical diagnosis - Triple-phase bone scan - MRI to rule out other conditions	- **Compartment pressure measurement**: ≥30 mmHg is diagnostic - Physical examination
Treatment	- Pain management: NSAIDs, opioids, gabapentinoids - Physiotherapy, occupational therapy - Sympathetic nerve blocks, spinal cord stimulation in severe cases	**Surgical fasciotomy**: Immediate decompression is critical to prevent permanent damage
Complications	- Chronic disability - Muscle atrophy - Depression and anxiety	- Permanent nerve and muscle damage - Rhabdomyolysis - Limb amputation in severe cases
Prognosis	Variable; some patients improve while others develop chronic symptoms	Good with timely intervention; delayed treatment may result in permanent deficits
Key Differentiator	Pain and autonomic dysfunction out of proportion to the initial injury	Pain due to raised pressure in a compartment that can progress to ischemia

Acute compartment syndrome is a surgical emergency and requires an early fasciotomy.
Elevated positioning may worsen ischemia by reducing blood flow.

A repeat X-ray is the most appropriate next investigation looking for patchy osteoporosis in patient developed clinical features consistent with complex regional pain syndrome type 1 (CRPS1)

Cryoglobulinaemia

Definition:

- Cryoglobulinaemia is a disorder characterized by the presence of cryoglobulins—immunoglobulins that precipitate at cold temperatures and dissolve upon warming—in the blood.

Pathophysiology:

- **Type I**: Monoclonal immunoglobulins, usually associated with haematologic malignancies (e.g., multiple myeloma).
- **Types II and III (Mixed Cryoglobulinaemia)**: Contains polyclonal IgG along with monoclonal or polyclonal IgM, with rheumatoid factor activity. These types are often related to chronic infections (especially **Hepatitis C**), autoimmune diseases, or lymphoproliferative disorders.

Types of Cryoglobulinaemia (Comparison Table)

Feature	Type I	Type II (Mixed)	Type III (Mixed)
Immunoglobulins	Monoclonal (IgG or IgM)	Polyclonal IgG + Monoclonal IgM (with RF activity)	Polyclonal IgG + Polyclonal IgM (with RF activity)
Association	Haematologic malignancies (e.g., multiple myeloma)	Hepatitis C, autoimmune diseases	Chronic infections, autoimmune diseases
Clinical Features	Hyperviscosity, Raynaud's, ulcers	Palpable purpura, glomerulonephritis, neuropathy	Palpable purpura, arthralgia, neuropathy
Complement Levels	Normal	Decreased (C4)	Decreased (C3 and C4)
Prevalence	Rare	Most common	Less common than Type II
Example	Multiple Myeloma	Hepatitis C infection	Autoimmune diseases (e.g., Sjögren's syndrome)

Clinical Features:

- **Skin**: Palpable purpura, ulcers, necrosis.
- **Renal**: Glomerulonephritis (hematuria, proteinuria, renal failure).
- **Neurological**: Peripheral neuropathy (paresthesia, weakness).
- **Musculoskeletal**: Arthralgia, myalgia.
- **Systemic**: Fatigue, fever.

Complications:

- Renal failure.
- Vasculitis with ischemic tissue damage.
- Lymphoproliferative disorders.
- Chronic hepatitis C infection in mixed cryoglobulinaemia.

Diagnostic Criteria:

- **Laboratory**:
    - Serum cryoglobulin detection.
    - Complement levels (decreased C4 and C3 in mixed types).
    - Rheumatoid factor (positive in mixed cryoglobulinaemia).
- **Kidney Biopsy** (if renal involvement): Membranoproliferative glomerulonephritis.
- **Hepatitis Serology**: Screening for Hepatitis C infection.

Treatment:

Treatment	Mode of Action	Dose / Examples	Side Effects / Contraindications
Corticosteroids	Immunosuppression	Prednisolone 0.5-1 mg/kg/day	Weight gain, hyperglycaemia, osteoporosis
Plasmapheresis	Removes circulating cryoglobulins	Sessions as needed	Hypotension, infections
Immunosuppressants	Suppresses immune response	Rituximab (anti-CD20 antibody)	Infection risk, infusion reactions
Antiviral Therapy	Treats Hepatitis C (if present)	Sofosbuvir + Ribavirin	Anaemia, fatigue, teratogenicity (Ribavirin)

Key Points for MRCP Candidates:

- Mixed cryoglobulinaemia is closely linked with **Hepatitis C** infection.
- **Palpable purpura** is a hallmark skin manifestation.
- Renal involvement manifests as **membranoproliferative glomerulonephritis**.
- **Low C4 levels** are typically found in mixed cryoglobulinaemia.
- Management involves immunosuppression and treating the underlying cause (e.g., antivirals for Hepatitis C).

Definition:

Cryoglobulinaemia is a disorder involving abnormal serum immunoglobulins (cryoglobulins) that precipitate at cold temperatures (<37°C) and dissolve upon warming. These immune complexes can deposit in small vessels, causing **vasculitis**, immune-mediated damage, and hypocomplementemia.

Pathophysiology:

- **Cryoglobulins** are usually **IgM** directed against the Fc region of IgG.
- They precipitate at **low temperatures** (peak precipitation at +4°C) and dissolve upon rewarming.
- Female-to-male ratio is **3:1**.
- Immune complex deposition in small vessels → **vasculitis** with thrombosis, leading to **gangrene** in extremities.
- Activation of the complement system by immune complexes results in **low complement levels** (hypocomplementemia).
- Causes **small-vessel vasculitis**, contributing to **axonal peripheral neuropathy**.

Causes:

- **Idiopathic** (one-third of cases)
- **Infections**: Hepatitis C, Hepatitis B, Epstein-Barr virus, cytomegalovirus
- **Haematologic malignancies**: Multiple myeloma, chronic lymphocytic leukaemia (CLL), Waldenström's macroglobulinemia
- **Autoimmune diseases**: SLE, Rheumatoid arthritis (RA), Sjögren's syndrome

Types of Cryoglobulinaemia (Comparison Table)

Type	Immunoglobulins	Associations	Clinical Features	%	Complement Levels
Type I	Monoclonal (IgG or IgM)	Haematologic malignancies (multiple myeloma, CLL, Waldenström's macroglobulinemia)	Hyperviscosity, Raynaud's, ulcers	25%	Normal
Type II	Mixed: Monoclonal IgM RF + Polyclonal IgG	Hepatitis C, infections (EBV, CMV, endocarditis), autoimmune diseases (SLE, RA)	Palpable purpura, glomerulonephritis, neuropathy	25%	Decreased (C4)
Type III	Mixed: Polyclonal IgM RF + Polyclonal IgG	Autoimmune diseases (RA, Sjögren's), chronic infections	Purpura, arthralgia, neuropathy	50%	Decreased (C3 and C4)

Symptoms and Signs (if Cryoglobulins are in High Concentrations)

- **Meltzer's Triad**: Palpable purpura, arthralgia, myalgia (common in Types II/III)
- **Cutaneous**: Purpura, livedo reticularis, Raynaud's phenomenon, acrocyanosis, distal ulceration
    - **Skin** is the most frequently involved organ (>90%)
- **Musculoskeletal**: Arthralgia (seen in 70%)
- **Renal**: Diffuse glomerulonephritis (common in Types II and III; occurs in 50% of cases)
- **Neurological**: Axonal peripheral neuropathy (polyneuropathy occurs in 40%)
- **GIT**: Abdominal pain, hepatomegaly (in 30% of cases)
- **Respiratory**: Dyspnoea, cough
- **Vascular**: Hypertension, pulmonary embolism, ischemic ulcers, arterial and venous thrombosis

Diagnostic Tests:

- **Serum cryoglobulins**: Sample tubes must be pre-warmed to 37°C to avoid false negatives.
- **Complement levels**: Low C4 in 90% of cases with mixed cryoglobulinaemia (Type II).
- **Rheumatoid factor (RF)**: Positive in mixed types.
- **ESR**: Elevated.
- **Hepatitis C serology**: If negative, check for HCV RNA via PCR.
- **Kidney biopsy**: Membranoproliferative glomerulonephritis in renal involvement.

Treatment:

Therapy	Indication	Examples	Side Effects / Notes
Immunosuppression	Severe disease or organ involvement	High-dose steroids + cyclophosphamide	Weight gain, infections, bone marrow suppression
Plasmapheresis	Rapid symptom control, removes circulating cryoglobulins	Sessions as needed	Hypotension, infections
Antiviral therapy	Hepatitis C-associated cryoglobulinaemia	Interferon-alpha	Fatigue, flu-like symptoms
Rituximab	For severe or refractory cases	Anti-CD20 monoclonal antibody	Infusion reactions, increased infection risk

Key Points:

- **Mixed cryoglobulinaemia (Types II and III)** makes up **80% of cases** and is strongly associated with **Hepatitis C**.
- A combination of **low C4** and a **positive rheumatoid factor** (RF) can support diagnosis.
- **Membranoproliferative glomerulonephritis** is a hallmark finding on renal biopsy.
- A vasculitic rash with neuropathy in a patient with **Hepatitis C** is highly suggestive of cryoglobulinaemia.

Consumption of C4 + strongly positive rheumatoid factor → cryoglobulinaemia.

Hepatitis C is the most common cause of cryoglobulinemia.

Overall, 50% of hepatitis C patients have cryoglobulins, but only 5% develop cryoglobulinemic vasculitis.

Most importantly, hepatitis C infection should always be excluded.

- If serological testing is negative, then the cryoprecipitate should be checked for HCV RNA by PCR.
- **Membranoproliferative glomerulonephritis (also known as mesangiocapillary glomerulonephritis) is the characteristic histological finding on biopsy where there is renal involvement.**
- For hepatitis C associated mixed cryoglobulinaemia, **Interferon alpha is the treatment of choice**, although rapidly progressive disease may require immunosuppressive therapy.

Mixed cryoglobulinemia (type II and III cryoglobulinemia) →80% of all cryoglobulins

- Have positive rheumatoid factor.
- A positive RF and low C4 ("poor man's cryo") level supports the diagnosis before the cryoglobulin screen has returned
- Closely associated with hepatitis C virus (HCV)

Most patients with mixed cryoglobulinemia will present with palpable purpura, arthralgia, and weakness/myalgias (Meltzer's triad), seen in one third of patients.

Meltzer's triad (seen in cryoglobulinaemia (types II/III) → palpable purpura, arthralgia and myalgia

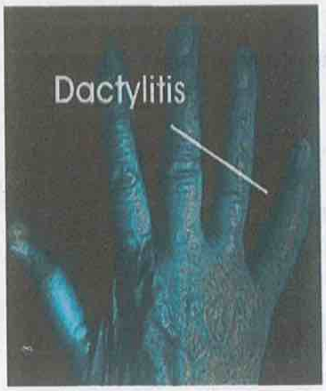
A vasculitic rash and neuropathy in a patient with hepatitis C is suggestive of cryoglobulinaemia.

Hypocomplementemia is seen in many conditions, including:

- Lupus
- **Mixed cryoglobulinemia**
- Membranoproliferative glomerulonephritis
- Hereditary angioedema.

Dactylitis

- Dactylitis describes the inflammation of a digit (finger or toe).
- **A 'sausage-shaped' digit is a classical description of dactylitis**
- **Causes** include:
  - ⇨ spondyloarthritis: e.g. **Psoriatic** and **reactive arthritis**
  - ⇨ sickle-cell disease
  - ⇨ other rare causes include tuberculosis, sarcoidosis and syphilis



De Quervain's tenosynovitis

Aspect	Details
Definition	A painful condition caused by inflammation of the tendons of the first extensor compartment, particularly the abductor pollicis longus (APL) and extensor pollicis brevis (EPB).
Pathop'.ysiology	- Repetitive thumb or wrist movements lead to microtrauma. - Inflammation of the tendon sheaths restricts tendon movement within the synovial sheath, causing pain and swelling.
Clinical Features	- Pain on the radial side of the wrist, especially during thumb or wrist movements. - Swelling near the base of the thumb. - Positive **Finkelstein's test**: Pain elicited when the thumb is flexed and the wrist is ulnarly deviated.
Complications	- Chronic pain or swelling. - Decreased grip strength. - Functional limitation in wrist or thumb movements.
Diagnostic Criteria	Clinical diagnosis based on history, physical exam (positive Finkelstein's test), and tenderness/swelling over the radial styloid. Imaging is usually not required.
Treatment	**Conservative**: - Rest, thumb spica splinting, and avoidance of aggravating activities. - NSAIDs for pain relief. - Steroid injections into the tendon sheath for inflammation. **Surgical** (if conservative management fails): - Release of the first extensor compartment to relieve tendon entrapment.
Findings in Labs and Imaging	- Not routinely required. - Ultrasound can show tenosynovitis or thickened tendons if needed for diagnosis.
Key Drugs	**NSAIDs**: - *Examples*: Ibuprofen (200–400 mg every 4–6 hours), Naproxen (250–500 mg twice daily). - **Side effects**: GI irritation, renal dysfunction. - **Contraindications**: Peptic ulcer disease, renal impairment. **Corticosteroids**: - *Example*: Methylprednisolone injection. - **Side effects**: Local pain, risk of tendon rupture if overused.

Monoarticular arthritis

	Acute Monoarticular Arthritis	Chronic Monoarticular Arthritis (>6 weeks)
Inflammatory	▪ Septic ▪ Crystal deposition diseases (Gout , Pseudogout)	▪ Mycobacterial infection ▪ Fungal infection ▪ Lyme arthritis ▪ Monoarticular presentation of rheumatoid arthritis ▪ Seronegative spondyloarthritis ▪ Sarcoid arthritis
Noninflammatory	▪ Coagulopathy (Hemarthrosis) ▪ Avascular necrosis of bone	▪ Osteoarthritis ▪ Avascular necrosis of bone ▪ Pigmented villonodular synovitis ▪ Lipoma arborescens ▪ Neuropathic (Charcot joint) ▪ Synovial chondromatosis ▪ Synovioma

Key points

1. **Most common diagnoses in acute monoarticular arthritis: crystalline, septic, osteoarthritis, trauma.**

2. **Most important diagnostic test in acute monoarticular arthritis: synovial fluid analysis and culture.**

3. **Most important diagnoses to rule out in chronic monoarticular arthritis: indolent infection and tumor.**

4. **Best diagnostic tests in chronic monoarticular arthritis: synovial fluid analysis, radiograph, magnetic resonance imaging (MRI), arthroscopy with synovial biopsy and culture.**

the most likely diagnoses in hospitalized patients who develop acute monoarticular arthritis following admission for another medical or surgical disease → Acute gout, pseudogout, and infection.

History	Probable diagnosis
Several hours to 2 days onset?	Infection, crystal diseases, inflammatory arthritis
Insidious onset over weeks?	Indolent infections, osteoarthritis, tumor
Intravenous drug abuse, or recent infection of any kind?	Infection
Prior episodes of acute joint pain and swelling?	Crystal diseases
Bleeding diathesis, or use of anticoagulants?	Hemarthrosis
Prolonged course of glucocorticoids?	Infection, avascular necrosis

Gout

Aspect	Details
Pathophysiology	- Deposition of **monosodium urate crystals** in synovial fluid and tissues triggers local inflammation (microcrystal synovitis), arthritis, and joint deformities. - Can occur even with normal uric acid levels.
Causes	- **Decreased uric acid excretion** (most common, 90%): Due to chronic renal insufficiency, or medications (e.g., thiazides, aspirin, loop diuretics). - **Increased uric acid production**: High cell turnover (tumour lysis syndrome, psoriasis), enzyme defects (Lesch-Nyhan syndrome), high-purine diet, obesity, or metabolic disorders. - **Combined mechanism**: Alcohol consumption affects both excretion and production. - **Primary hyperuricemia**: Idiopathic or genetic causes like Lesch-Nyhan syndrome.
Features	- **Acute gouty arthritis**: Sudden onset monoarthritis, often in the first metatarsophalangeal joint (big toe); redness, swelling, and severe pain. - **Chronic gout**: Progressive joint destruction, tophi (urate crystal deposits) formation in soft tissues, uric acid nephrolithiasis, and nephropathy.
Investigations	- **Blood tests**: Elevated white blood cell count (WBC), ESR, and often elevated serum uric acid (but can be normal). - **Joint aspiration (gold standard)**: Presence of negatively birefringent, needle-shaped monosodium urate crystals. - **X-ray findings**: Punched-out erosions with overhanging edges (rat-bite erosions). - **Advanced imaging**: Dual-energy CT or ultrasound for detecting tophi.
Management	**Lifestyle modifications**: Weight loss, reduced alcohol, low-purine diet (avoid red meat, seafood). **Acute flare treatment**: - **NSAIDs**: First-line unless contraindicated (e.g., renal or GI issues). - **Colchicine**: 1.2 mg initially, followed by 0.6 mg after 1 hour, then 0.6 mg twice daily until 48 hours after resolution. - **Glucocorticoids**: Prednisolone (40 mg/day, tapered over 10 days) for patients with contraindications to NSAIDs or colchicine. - **IL-1 antagonists**: Anakinra or canakinumab for refractory cases.

Aspect	Details
Chronic Management	- **Urate-lowering therapy (ULT)**: **First-line**: Xanthine oxidase inhibitors (Allopurinol 100–800 mg/day or Febuxostat 40–120 mg/day). **Second-line**: Uricosurics (Probenecid). **Third-line**: Pegloticase for refractory cases. **Indications for ULT**: Tophi, chronic joint damage, ≥2 gout attacks/year, or CKD ≥ stage 3. - **Prophylaxis during ULT initiation**: Colchicine or NSAIDs to prevent flares.
Target urate level	- Target urate level: <6 mg/dL (360 μmol/L) or <5 mg/dL (297 μmol/L) in tophaceous gout cases.
Drug Mechanism & Side Effects	- **Allopurinol**: Inhibits xanthine oxidase; risk of hypersensitivity (avoid with HLA-B*5801 allele). - **Febuxostat**: Xanthine oxidase inhibitor; associated with cardiovascular risks. - **Probenecid**: Uricosuric agent; increases uric acid excretion. - **Pegloticase**: Converts uric acid to allantoin (water-soluble); infusion reactions may occur.
Special Considerations	- **Coexisting Hypertension**: Losartan has uricosuric effects. - **Hyperlipidemia**: Atorvastatin may reduce uric acid levels.
Prognosis	- Gout is associated with an increased risk of cardiovascular morbidity and mortality.

Lesch-Nyhan syndrome

- **Hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency**
- X-linked recessive therefore only seen in boys
- **Features:** gout, renal failure, neurological deficits, learning difficulties, aggressiveness, self-mutilation (for example, biting of finger tips and/or lips).

There is well defined **punched-out** juxta-articular erosions related to both sides of the first metatarsal bone. This is a classical site for gout.

Acute gout flare treatment

Without renal, cardiovascular or active GIT comorbidities	NSAIDs
End-stage kidney disease and transplantation	Prednisolone 40 mg daily until the flare resolves, tapered over 10 days or intraarticular steroid injection.
Patients on anticoagulation	1st line: Colchicine 2nd line: Glucocorticoids 3rd line: Celecoxib
Pregnant women	1st line: Oral glucocorticoid. 2nd line (If steroid is contraindicated) → NSAIDs in the first 20 weeks of gestation or colchicine.
Breastfeeding women	NSAIDs or glucocorticoids. Avoid colchicine.
Refractory disease	Anakinra (IL-1 antagonist): 100 mg daily, subcutaneously daily until flare resolution. Canakinumab 150 mg single dose subcutaneously; may be repeated at intervals of ≥12 weeks

Acute gout flare treatment

NSAIDs	Contraindicated in renal impairment, GIT bleed, and patients taking warfarin	Naproxen (500 mg twice daily) or indomethacin (50 mg three times daily) or ibuprofen (800 mg three times daily)
Colchicine	▪ Useful in patients taking warfarin ▪ Can be used in mild and moderate CKD ▪ Contraindicated in Severe CKD	initially 1.2 mg and 0.6 mg one hour later, then 0.6 mg twice daily
Glucocorticoids	▪ Preferable in CKD , pregnancy or lactation ▪ Avoid in DM or HTN	Prednisolone 40 mg daily until the flare resolves, tapered over 10 days
IL-1 antagonist	▪ For refractory disease	▪ Anakinra (100 mg SC daily) ▪ Canakinumab 150 mg SC single dose

Monitor for myotoxicity when prescribing colchicine with statins. Reduce dose of pravastatin, atorvastatin, and simvastatin when prescribed concomitantly.

Urate-lowering therapy

	First-line Xanthine oxidase inhibitors (XOIs)	Second-line Uricosurics	Third-line Recombinant uricase
Drug	▪ Allopurinol (preferred 1st line) ▪ Febuxostat (alternative 1st line when allopurinol has not been tolerated or is contraindicated.)	Probenecid	Pegloticase
Mechanism of action	Inhibition of xanthine oxidase	Inhibition of uric acid reabsorption along renal proximal convoluted tubules → increased renal elimination	breakdown of uric acid to allantoin (allantoin is water-soluble and therefore can be renally excreted)
Side effects	**Allopurinol:** rash , Stevens-Johnson syndrome/toxic epidermal necrolysis **Febuxostat:** Nausea, diarrhea, transaminitis	▪ Urolithiasis (uric acid stones) ▪ Hypersensitivity reactions (sulfa allergy due to being a sulfonamide derivative)	Infusion reactions, including anaphylaxis
Specific contraindications	**Allopurinol:** Presence of HLA-B*5801 allele →↑the risk of hypersensitivity reaction (Black patients and those of Southeast Asian) **Febuxostat:** CVD disease	▪ Nephrolithiasis ▪ Moderate to severe CKD	▪ G6PD deficiency ▪ Congestive heart failure
Interactions	▪ Purine analogs (e.g., azathioprine, 6-mercaptopurine) + XOIs can → bone marrow toxicity ▪ Probenecid and thiazides decrease the efficacy of allopurinol ▪ Allopurinol →↑ INR by inhibiting the metabolism of warfarin.	Inhibits penicillin secretion in the proximal convoluted tubule	Should not be used concomitantly with XOIs or uricosurics.

Urate-lowering therapy

1st line: Xanthine oxidase inhibitors

- Allopurinol (100 mg once daily, increased by 100 mg increments every 2 weeks up to maximum 800 mg/day). Alternative: unable to take or intolerant of allopurinol: febuxostat (40 mg once daily; may increase by 40 mg every 2 weeks up to120 mg once daily).

2nd line: Uricosuric Agent

- Probenecid (250 mg twice daily for 1 week, followed by 500 mg twice daily; may increase dose by 500 mg every 4 weeks)

Coexistent hypertension and gout

- Antihypertensive either increase serum **uric acid levels** (e.g., diuretics, β-**blockers**) or **decrease** serum **uric acid levels** (e.g., **calcium-channel blockers**, **losartan**).
- **Losartan** has a specific uricosuric action (↑excretion of uric acid in the urine, →↓serum uric acid).

Coexistent hyperlipidemia and gout

- Atorvastatin is the only statin with a urate-lowering effect

Targeted urate-lowering range

- <6 mg/dL (<357 micromol/L) or, in the case of patients with tophaceous gout, <5 mg/dL (<297 micromol/L).

The vast majority of gout is due to decreased renal excretion of uric acid

Gout: start allopurinol if >= 2 attacks in 12 month period

Drugs associated with gout: aspirin, thiazides, niacin, pyrazinamide, loop diuretics.

What is the <u>most common cause</u> of acute gout in association with G-6PD deficiency?

- **Increased production of pentose sugars**
  - Glucose-6-phosphate dehydrogenase (G6PD) → converts (G6P) to glucose.
  - (G6PD) Deficiency → accumulation of G6P → enters the hexose monophosphate shunt → ↑ **production of pentose sugars**. (These act as a substrate for phosphoribosyl pyrophosphate (PRPP) synthetase) → ↑ **production of purines** → uric acid.
  - Hypoglycaemia in G6PD deficiency →↑ catecholamine levels → ↑glycogenolysis in muscles →↑ lactic acidosis → ↓urate excretion (competes with uric acid for excretion)

Low-dose aspirin can decrease uric acid excretion and trigger recurrent gout flares but it should not be stopped in patients taking it for specific indications (e.g., coronary artery disease, cerebrovascular disease), regardless of the severity of gout.

Monitor for myotoxicity when prescribing colchicine with statins. Reduce dose of pravastatin, atorvastatin, and simvastatin when prescribed concomitantly.

The combination of allopurinol and azathioprine leads to increased bone marrow toxicity

Antihypertensive drugs and gout

- Antihypertensive either increase serum **uric acid levels** (e.g., diuretics, β-**blockers**) or **decrease** serum **uric acid levels** (e.g., **calcium-channel blockers**, **losartan**).
- Losartan has a specific uricosuric action (↑excretion of uric acid in the urine, thus reducing the serum uric acid) and may be particularly suitable for the many patients who have coexistant hypertension

Pseudogout

Definition

- Pseudogout is a form of microcrystal synovitis **caused by the deposition of calcium pyrophosphate dihydrate in the synovium**

Risk factors

- Hyperparathyroidism, hypothyroidism
- Haemochromatosis, acromegaly, Wilson's disease
- low magnesium, low phosphate

Features

- **Most commonly affects the knee and wrist.**
- **Joint aspiration:** positively birefringent **rhomboid-shaped crystals**. Synovial fluid findings: 10,000-50,000 WBCs/μL with > 90% neutrophils
- **Joint x-ray: chondrocalcinosis** (calcification of cartilage in the affected joints)

Management

- Aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

Osteoarthritis (OA)

Pathogenesis: localised loss of cartilage, with remodelling of adjacent bone.

Risk factors: Obesity (the commonest causes), haemochromatosis (secondary OA)

Features

- Pain is exacerbated by exercise and relieved by rest, although in advanced disease rest and night pain can develop.
- **Joint swelling is bony in nature**, unlike the boggy swelling which occurs in inflammatory arthritis.
- Characteristically affects the **distal interphalangeal**, interphalangeal and first metacarpophalangeal joints. The trapezio-metacarpal joint (base of thumb) is the most common site.

X-ray changes of osteoarthritis
- decrease of joint space
- subchondral sclerosis
- subchondral cysts
- osteophytes forming at joint margins

Management
- 1st line: paracetamol and topical NSAIDs (if knee or hand)
- 2nd line: oral NSAIDs/COX-2 inhibitors.
- 3rd line: duloxetine (for multiple joint, if NSAIDs are ineffective or contraindicated)
- Definitive treatment: joint replacement

Septic arthritis

Causes
- The most common organism is *Staphylococcus aureus*. Gonococcal arthritis is the most common form of arthritis in sexually active young adults.

Feature
- Classical triad of fever, joint pain, and restricted range of motion. Joints are swollen, red, warm, and painful. Usually monoarticular.
- Associated bacteraemia in 50%

Diagnosis
- Any red, painful joint with a reduced range of motion should be considered infectious until proven otherwise.
- Arthrocentesis with synovial fluid analysis and culture (gold standard): ↑ WBC count (e.g., > 50,000/mm3)
- X-rays of the affected joint. Early x-rays are almost always normal.
- Inflammatory markers may be normal in septic arthritis

Management
- Synovial fluid should be obtained before starting treatment
- Intravenous antibiotics: which cover Gram-positive cocci are indicated. The BNF recommends flucloxacillin or clindamycin if penicillin allergic
- **Antibiotic duration:** BNF states 6-12 weeks.
- Needle aspiration should be used to decompress the joint
- Surgical drainage may be needed if frequent needle aspiration is required

Antibiotic Guidelines for Septic Arthritis (BNF-guidelines)

Initial Management:
- **Joint aspiration** is critical for diagnosis. It allows for synovial fluid analysis, including Gram stain, culture, and cell count, which guide antibiotic therapy.
- Empiric antibiotics should begin promptly after sample collection to cover likely pathogens, particularly *Staphylococcus aureus* and streptococci.

Empirical Antibiotic Therapy:

- **Vancomycin (IV)**: Recommended if methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected.
- **Flucloxacillin (2g QDS IV)**: First-line for methicillin-sensitive *Staphylococcus aureus* (MSSA). Can switch to oral flucloxacillin (1g QDS) upon clinical improvement.
- **Ceftriaxone (2g once daily IV)**: Used in cases where gram-negative pathogens or gonococcal infection is a concern.

Antibiotic Selection Based on Patient Factors:

- **Penicillin Allergy**: Doxycycline (200 mg once daily) or clindamycin may be used.
- **History of MRSA**: Vancomycin remains the preferred option, but specialist input may be required.
- **Duration**: Typically, antibiotics are administered for **2–6 weeks** based on the clinical response and culture results, with a transition from IV to oral therapy recommended when appropriate.

Any patient with fever, arthralgias, and tenosynovitis should be evaluated for a disseminated gonococcal infection (DGI).

The majority of females develop DGI within 1 week of onset of menses and genitourinary symptoms may be absent.

Avascular necrosis (AVN)

Definition: death of bone tissue due to interruption of blood supply; most commonly affects the epiphysis of long bones such as the femur.

Causes

- **Long-term steroid use**
- **Sickle cell disease**, Gaucher disease
- Cellular toxicity (e.g., **chemotherapy**, radiotherapy, alcohol excess)
- Trauma

Features

- Initially asymptomatic
- Pain in the affected joint

Investigation

- Plain x-ray findings may be normal initially
- **MRI is the investigation of choice.** It is more sensitive than radionuclide bone scanning

Treatment: Joint replacement (e.g., hip, shoulder, knee)

Paget's disease of the bone

Epidemiology

- Second most prevalent skeletal disease after osteoporosis
- Prevalence: 1–2% of individuals > 55 years. more common in men.

Pathophysiology

- Focal bone remodelling disorder (↑uncontrolled bone turnover) → ↑↑osteoclasts → ↑↑bone resorption →↑new bone formation and altered bone architecture (weak, disorganized new bone formation) → liable to pathological fracture and deformity. **the pelvis is the most commonly** affected.

Risk factors: increasing age, male sex. northern latitude, family history

Features

- **Asymptomatic (most common):** detected incidentally on radiographs and laboratory isolated ALP elevation.
- **Bone pain** (e.g. pelvis, lumbar spine, femur), **typically increased with rest and on weight bearing.**
- **Bowing of tibia, bossing of skull**

Complications

- **Deafness** (8th cranial nerve entrapment in the skull)
- **Pathological fractures,** spinal cord compression
- **Skull thickening** (a classic symptom: a hat which no longer fits)
- **High-output cardiac failure** (due to AV shunts in bone)
- **Bone sarcoma** (1% if affected for > 10 years)
  - ⇨ Most common primary bone malignancy, arising from osteoblasts, presented with localised pain and pathological fracture. X-ray: **sunburst appearance of lytic bone lesions**. Treatment: Surgery (definitive resection) with adjuvant polychemotherapy. Usually resistant to radiation therapy

Diagnosis

- **Initial test** → Raised alkaline phosphatase (ALP) + normal **calcium and phosphate**
- **X-ray:** eg: (skull x-ray) → osteolysis and new bone formation, bone expansion, cortical thickening and **trabecular bone thickening**.
- **Skeletal survey → Confirmatory test**
- **Bone biopsy:** abnormal **"mosaic"** pattern in woven and lamellar bone.

Treatment

- **Indications for treatment: bone pain, skull or long bone deformity, fracture, or periarticular Paget's**
- **1st line: bisphosphonate (oral risedronate or IV zoledronate)** → **relieve pain** and **↓risk of pathological fracture** in long bones **and complications of Paget's such as deafness**.
- **2nd line:** calcitonin
- **Monitoring → 6-monthly alkaline phosphatase levels**

The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.

A combination of bony pain, unilateral hearing loss, and an isolated raised ALP in older patient→ Paget's disease of the bone.

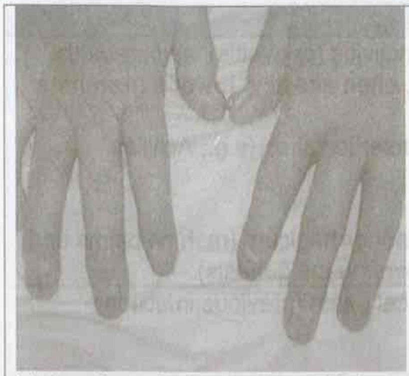
Psoriatic arthropathy

Aspect	Details
Overview	- Chronic, progressive seronegative inflammatory arthritis associated with psoriasis. - Affects both men and women equally, with onset typically between **ages 35-55**.
Epidemiology	- Around **10-20%** of patients with psoriasis develop psoriatic arthritis. - Psoriatic arthritis can **precede or follow** skin lesions.
Genetics	- Increased frequency of **HLA-B7 and HLA-B27** alleles.
Types of Psoriatic Arthritis	1. **Asymmetric oligoarthritis** (most common, 43%). 2. **Symmetric polyarthritis** (33%). 3. **Sacroiliitis**. 4. **DIP joint disease**: Associated with nail pitting and onycholysis. 5. **Arthritis mutilans**: Rare, severe deformities ("telescoping fingers").
Clinical Features	- **Dactylitis** ("sausage digits") in 35% of patients. - **Nail involvement**: Onycholysis, pitting, and ridging. - **Vertebral involvement**: Asymmetrical, sometimes involving atlantoaxial subluxation. - **Extra-articular features**: Ocular involvement (conjunctivitis, uveitis), synovitis, and enthesitis (tendon inflammation).
Investigations	- Elevated **ESR** and **CRP**. - **Rheumatoid factor (RF)** negative. - **Radiography**: "Pencil-in-cup" deformities in DIP joints.

Aspect	Details
Diagnostic Criteria	- Requires inflammatory arthritis with **≥3 points** from the following: 1. Current psoriasis (2 points). 2. History of psoriasis (1 point). 3. Family history of psoriasis (1 point). 4. Dactylitis (1 point). 5. Juxta-articular new bone formation (1 point). 6. RF negativity (1 point). 7. Nail dystrophy (1 point).
Differential Diagnosis	- **Ankylosing spondylitis**: Different sacroiliitis pattern, no skin/nail involvement. - **Rheumatoid arthritis**: Absence of anti-cyclic citrullinated peptide antibodies and presence of dactylitis suggest psoriatic arthritis.
Management	- **Mild disease**: NSAIDs for symptom relief (do not prevent joint damage). - **Moderate-to-severe disease**: DMARDs like **methotrexate** (improves both joint and skin symptoms). - **Second-line**: TNF-alpha inhibitors if DMARDs fail. - **Apremilast** (PDE4 inhibitor): Used if unresponsive to ≥2 DMARDs. - **Sulfasalazine**: Safe in pregnancy but affects joints more than skin.
Cautions	- **Hydroxychloroquine** may worsen skin lesions. - **Systemic corticosteroids** can cause flares or induce pustular psoriasis upon withdrawal.
Prognosis	- Better prognosis than rheumatoid arthritis but still requires aggressive treatment for joint protection.

Inflammation of the DIP joints and finger dactylitis are highly characteristic of psoriatic arthritis.

Differential diagnosis of DIP arthritis: psoriatic, OA, multicentric reticulohistiocytosis, and primary biliary cirrhosis. In a patient with OA who gets inflamed DIP–rule out gout.



Notice the nail changes on this image as well

X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.

Reactive arthritis (Reiter syndrome)

Aspect	Details
Definition	Reactive arthritis (Reiter syndrome) is an **autoimmune condition** characterized by arthritis that develops in response to a prior infection (typically gastrointestinal or genitourinary).
Common Triggers	- **Gastrointestinal infections**: *Salmonella, Shigella, Yersinia, Campylobacter*. - **Genitourinary infections**: *Chlamydia trachomatis*.
Pathophysiology	- An infection triggers a cross-reactive immune response, resulting in inflammation affecting the joints, eyes, and urethra.
Epidemiology	- Commonly affects **young adults** (ages 20–40). - More prevalent in men following genitourinary infections and in both sexes following gastrointestinal infections. - Associated with **HLA-B27** gene in many cases.

Aspect	Details
Clinical Features	- **Triad of symptoms**: Arthritis, conjunctivitis (or uveitis), and urethritis. - **Arthritis**: Asymmetric, oligoarticular, often affecting **lower extremities** (knees, ankles). - **Enthesitis**: Inflammation at tendon insertion sites (e.g., Achilles tendon). - **Dactylitis** ("sausage digits"). - Skin manifestations: Keratoderma blennorrhagicum (rash on palms and soles), circinate balanitis (painless ulcers on the genitals).
Diagnosis	- Based on **clinical history** and physical exam (previous infection + characteristic features). - **Investigations**: **Elevated ESR and CRP**. HLA-B27 testing (may be positive). **Joint aspiration** to rule out septic arthritis. PCR or culture for Chlamydia or gastrointestinal pathogens.
Management	- **Antibiotics**: Only if active infection is present (e.g., Chlamydia). - **NSAIDs**: Mainstay for symptom relief. - **Corticosteroids**: For severe cases, either **intra-articular** or systemic. - **DMARDs** (e.g., methotrexate or sulfasalazine) for chronic or refractory arthritis.
Prognosis	- Symptoms usually resolve within **3-6 months** but may recur. - Chronic arthritis or spondylitis may develop in a minority of patients.
Complications	- Chronic arthritis or **spondyloarthropathy**. - Ocular complications (e.g., recurrent uveitis).

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

'Can't see, pee or climb a tree'

Urethritis + arthritis + conjunctivitis = reactive arthritis

Eye diseases in Reiter's syndrome:

- **Most common → conjunctivitis (50%)**
- **Less common → iritis (12%)**

Organisms that are most commonly associated with reactive arthritis:

Post-dysenteric form	Post-STI form
▫ *Shigella* flexneri ▫ *Salmonella typhi*murium ▫ *Salmonella* enteritidis ▫ *Yersinia enterocolitica* ▫ *Campylobacter*	*Chlamydia trachomatis*

Reactive arthritis is a sterile, inflammatory arthritis that is typically preceded by a gastrointestinal or genitourinary infection occurring 1 to 4 weeks previously.

The arthritis can improve with prolonged antibiotics only if it is due to Chlamydia.

Amyloidosis

Overview

- **Amyloidosis** refers to the extracellular deposition of insoluble fibrillar proteins, resulting in organ and tissue dysfunction.
- **Composition of amyloid**:
  - Amyloid fibrils, amyloid-P component (derived from serum amyloid P), apolipoprotein E, and heparan sulfate proteoglycans.

Causes

- **Inherited or Acquired**:
  - Inherited forms: Linked to genetic mutations.
  - Acquired forms: Often associated with chronic diseases (e.g., diabetes mellitus, rheumatoid arthritis).

Key Clinical Features

- **General symptoms**: Unexplained weight loss, fatigue, and edema resistant to diuretics.
- **Musculoskeletal**: Joint pain and stiffness, predominantly in the upper limbs.

Types of Amyloidosis and Features

Type	Cause	Features
Light-Chain Amyloidosis (AL)	Plasma cell dyscrasias (e.g., multiple myeloma, lymphoma).	- Heart: Restrictive cardiomyopathy, AV block. - Kidneys: Nephrotic syndrome, renal tubular acidosis. - Tongue: Macroglossia causing sleep apnea. - Neuropathy and carpal tunnel syndrome.

Type	Cause	Features
Reactive Amyloidosis (AA)	Chronic inflammatory or infectious diseases (e.g., IBD, tuberculosis).	- Kidney involvement (most common): Nephrotic syndrome, type II renal tubular acidosis. - Liver/Spleen: Hepatomegaly, splenomegaly. - Adrenal glands: Primary adrenal insufficiency.
β-2 Microglobulin Amyloidosis	Chronic dialysis	- Associated with neurological impairment and β-2 microglobulin deposition.

Diagnosis

- **Biopsy**: Fat, rectum, or salivary gland biopsies analyzed with **Congo red stain** (apple-green birefringence under light microscopy).
- **Tests for underlying disease**:
  - Serum electrophoresis and urine Bence-Jones proteins for AL amyloidosis.
  - ESR, CRP, and chest X-ray for AA amyloidosis.
- **Pathological characteristics**:
  - Beta-pleated sheet structure (electron micrography).
  - Amorphous eosinophilic appearance (H&E staining).

Cardiac Amyloidosis

- **Presentation**: Restrictive cardiomyopathy with signs of right heart failure (jugular venous distension, peripheral edema).
- **ECG Findings**: Low-voltage complexes with poor R wave progression.
- **Echocardiography**: Atrial dilation, diastolic dysfunction, and "speckled" myocardium appearance.

Management

- **Renal Amyloidosis**: Renal transplantation for end-stage kidney involvement.
- **Dialysis-related Amyloidosis**: Use high-flux dialysis membranes to reduce β-2 microglobulin buildup.
- **Cardiac Amyloidosis**: Avoid **digoxin** (risk of toxicity).
- **AL Amyloidosis**:
  - **Bone marrow transplant with stem cell rescue** (if tolerated).
  - **Chemotherapy**: Bortezomib, dexamethasone, or melphalan combinations.
- **AA Amyloidosis**: Management focuses on controlling the underlying chronic inflammatory disease.

Sjogren's syndrome

Definition

- Sjögren's syndrome is a **chronic autoimmune disease** characterized by inflammation primarily targeting the **exocrine glands**, leading to **dry eyes (keratoconjunctivitis sicca)** and **dry mouth (xerostomia)**. It can manifest as:

1. **Primary Sjogren's Syndrome**: Occurs independently without other autoimmune diseases.
2. **Secondary Sjogren's Syndrome**: Occurs alongside conditions such as **rheumatoid arthritis** or **systemic lupus erythematosus**.

Pathophysiology

- **Autoimmune attack** on lacrimal and salivary glands involves infiltration by lymphocytes (mostly CD4+ T-cells and B-cells), leading to glandular inflammation and dysfunction.
- **Autoantibodies** such as **anti-Ro/SSA** and **anti-La/SSB** contribute to tissue damage.
- Persistent inflammation can cause **fibrosis and atrophy** of the glands, extending to other organs, including the lungs and kidneys.
- Activation of the **innate immune system** increases cytokine levels, perpetuating the inflammatory response.
- There is a heightened risk of **lymphoma**, particularly non-Hodgkin lymphoma, among affected patients.

Clinical Features

- **Glandular Symptoms**:
  - Dry eyes, dry mouth, difficulty swallowing, and increased dental issues.
- **Extraglandular Involvement**:
  - **Musculoskeletal**: Fatigue and joint pain.
  - **Peripheral Neuropathy**: Tingling or numbness in extremities.
  - **Pulmonary/Renal**: Interstitial lung disease, interstitial nephritis.
  - **Lymphoma Risk**: 2-5% of patients develop non-Hodgkin lymphoma.

Diagnosis

- **Autoantibody testing**: Presence of **anti-Ro/SSA** and **anti-La/SSB** antibodies.
- **Ocular assessments**: Schirmer's test to measure tear production.
- **Salivary gland biopsy**: Confirms lymphocytic infiltration.
- **Ultrasound**: Useful to assess glandular function and damage.

Management

1. **Symptomatic Treatment**:
   - **Artificial Tears** and **saliva substitutes** for dry eyes and mouth.
   - **Pilocarpine**: 5 mg **four times daily** to stimulate salivary flow.
   - **Cevimeline**: 30 mg **three times daily** to increase gland secretion.
2. **Systemic Treatment**:
   - **Hydroxychloroquine**: 200–400 mg daily for musculoskeletal symptoms and fatigue.
   - **Methotrexate**: 7.5–25 mg weekly for systemic involvement.
   - **Rituximab**: 375 mg/m² IV weekly for 4 weeks, useful in refractory cases.
3. **Investigational Biologics**: New biologics are being studied for refractory cases, though no specific agents have yet been approved for routine use.

> **Sjögren's syndrome is the most common autoimmune disease in middle-aged women and should be considered in any patient with unexplained symptoms and a positive ANA**

Systemic lupus erythematosus (SLE)

Definition

- SLE is a **chronic multisystem autoimmune disease** characterized by the production of **autoantibodies** and immune complexes, leading to **inflammation and damage** across multiple organ systems.

Pathophysiology

- **Autoimmune response**: Production of autoantibodies (e.g., **anti-dsDNA, anti-Smith**) leads to immune complex formation and deposition in tissues.
- **Immune dysregulation**: Affects innate and adaptive immunity, causing inflammation and tissue injury.
- **Complement system activation**: Results in chronic inflammation, especially in kidneys (lupus nephritis).

Epidemiology

- **Prevalence**: 20-150 cases per 100,000 population, with higher rates among African American and Hispanic populations.
- **Age and gender**: Most commonly affects **women of childbearing age** (15-45 years).
- **Genetic and environmental factors**: Family history and environmental triggers (e.g., infections, ultraviolet light) contribute to disease onset.

Clinical Features

- **Constitutional symptoms**: Fatigue, fever, weight loss.
- **Skin manifestations**: Malar (butterfly) rash, discoid rash, photosensitivity.
- **Musculoskeletal**: Joint pain (non-erosive arthritis).
- **Renal involvement**: Lupus nephritis (proteinuria, hematuria).
- **Cardiopulmonary**: Pleuritis, pericarditis.
- **Neurological**: Seizures, psychosis.
- **Hematologic**: Anemia, leukopenia, thrombocytopenia.

Complications

- **Lupus nephritis**: Major cause of morbidity.
- **Cardiovascular disease**: Accelerated atherosclerosis and coronary artery disease.
- **Infections**: Due to immune suppression from the disease or medications.
- **Pregnancy complications**: Increased risk of miscarriage and preeclampsia.

Diagnosis

- **Laboratory tests**:
  - **ANA (antinuclear antibody)**: Sensitive but not specific.
  - **Anti-dsDNA** and **anti-Smith antibodies**: Specific for SLE.
  - **Complement levels**: C3 and C4 often decreased.
  - **Urinalysis**: To detect proteinuria and signs of nephritis.
- **Imaging and biopsy**: Renal biopsy in cases of suspected lupus nephritis.

Management

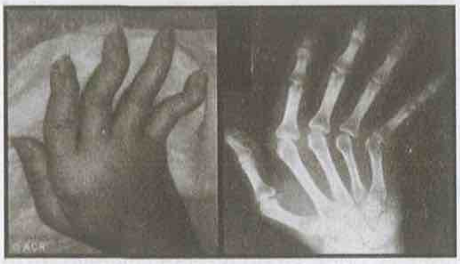
1. **General measures**:
   - Sun protection to avoid photosensitivity flares.
   - Vaccinations to prevent infections (e.g., influenza, pneumococcal vaccines).
2. **Medications**:
   - **Hydroxychloroquine**: 200-400 mg daily; reduces disease activity and prevents flares.
   - **NSAIDs**: For arthritis and pleuritic pain.

- **Glucocorticoids**: For acute flares; **prednisolone** 5-60 mg daily depending on severity.
- **Immunosuppressants**:
  - **Methotrexate**: 7.5-25 mg weekly for arthritis and systemic involvement.
  - **Azathioprine**: 1-3 mg/kg daily for maintenance therapy.
  - **Mycophenolate mofetil**: 1-3 g daily for lupus nephritis.
- **Biologic agents**:
  - **Belimumab**: Targets B-cells; used for refractory cases.
  - **Rituximab**: Effective for severe or refractory disease.

SLE - antibodies associated with congenital heart block = anti-Ro

SLE: C3 & C4 low

Jaccoud's Arthropathy



Jaccoud's arthropathy

- **defined as:** gross deformities of the hands without joint damage or erosions
- **caused by** recurrent episodes of synovitis that damage tendon sheaths and slings resulting in joint deformity
- **seen in:**
  - ⇨ SLE
  - ⇨ Rheumatic fever
  - ⇨ Parkinson's disease, and
  - ⇨ Hypocomplementaemic urticarial vasculitis.

SLE: ANA is 99% sensitive - anti-Sm & anti-dsDNA are 99% specific

Systemic Lupus Erythematosus (SLE) in Pregnancy:

Aspect	Details
Overview	- SLE tends to **worsen during pregnancy** and the **postpartum period** (puerperium). - Maternal **autoantibodies** may cross the placenta, leading to **neonatal lupus erythematosus**. - Neonatal complications include **congenital heart block**, especially associated with **anti-Ro (SSA) antibodies**.
Preferred Medication	**Azathioprine** - Safe for use in pregnancy with **evidence supporting** its use for rheumatological and gastrointestinal diseases. - **Less effective** for managing **renal involvement** in SLE, but preferred due to favorable **risk-benefit balance**.
Alternative Medication	**Ciclosporin** - Useful when **azathioprine** is insufficient for disease control. - **Risks**: Associated with **premature delivery** and **low birth weight**, though no significant link to congenital malformations.
Contraindicated Drugs	- **Cyclophosphamide** - **Methotrexate** - **Mycophenolate mofetil** **Reason**: High risk of **fetal harm** and congenital abnormalities.
Key Points	- **Preconception planning** and **close monitoring** during pregnancy are essential. - Focus on **balancing disease control** with **fetal safety**, avoiding teratogenic drugs.

Drug-Induced Lupus Erythematosus

Overview

- The **pathogenesis** of drug-induced lupus is not fully understood but may involve **drug metabolism variations** (e.g., acetylator status) and the generation of cytotoxic products by activated neutrophils.
- Typically **occurs in older adults (50–70 years)** and affects **men and women equally** (1:1 ratio).

Epidemiology

- More common in **Caucasians** compared to Afro-Caribbeans (inverse for idiopathic SLE).
- **Symptoms** appear within **3 weeks to 2 years** after initiating the offending drug.

Common Drugs Causing Lupus

1. **High-risk drugs**:
   - Procainamide, Hydralazine, Quinidine
2. **Low-risk drugs**:
   - Isoniazid, Sulfasalazine
3. **Other associated drugs**:
   - Minocycline, Phenytoin, Carbamazepine, Lamotrigine
   - **Anti-TNF agents**, Interferons, Statins

Risk Factors

- **Positive ANA** (antinuclear antibodies).
- **HLA-DR4** phenotype (hydralazine-induced lupus).

- **Slow acetylator status**: Increases the risk of lupus from hydralazine, procainamide, and isoniazid.
- **Large daily doses** of certain drugs.

Clinical Features

- **Common symptoms**:
  - Fatigue, fever, weight loss, joint pain (polyarthralgia), and myalgia.
  - **Pulmonary involvement** (e.g., pleurisy).
  - **Raynaud's phenomenon** (in 25% of cases).
- **Skin manifestations**:
  - Purpuric, erythematous papular rash (usually no malar or discoid rash).
  - Anti-TNF agents and interferons can cause **malar or discoid rash** and **anti-dsDNA positivity**.
- **Differences from idiopathic SLE**:
  - Rare renal, CNS, and hematological involvement.
  - Positive **antihistone antibodies** (95%) and negative **anti-dsDNA** antibodies.

Laboratory Features

- **ANA**: Strongly positive in all cases.
- **Anti-histone antibodies**: Positive in 95% of drug-induced cases.
- **Anti-dsDNA antibodies**: Usually negative.
- **CRP and ESR**: Markedly elevated.
- **C3/C4 complement levels**: Typically normal.

Comparison: Drug-Induced Lupus vs. Idiopathic SLE

Feature	Drug-Induced Lupus	Idiopathic SLE
Male ratio	1:1	10:1
Common ethnicity	Caucasians	Afro-Caribbeans
Age of onset	50–70 years	15–40 years
Renal, CNS involvement	Rare	Common
Anti-dsDNA antibodies	Rare	Common
Antihistone antibodies	Positive (95%)	50–80%
Complement levels (C3/C4)	Usually normal	Low in active disease
Treatment	Withdraw precipitating drug	Steroids and immunosuppressants

Treatment

- **Withdrawal of the offending drug** typically resolves symptoms.
- **Corticosteroids** or **DMARDs** may be required for symptom resolution in some cases.
- **Recovery** can take a few days to **two years** after stopping minocycline.

Prognosis

- **Spontaneous recovery** is common after discontinuing the causative drug.
- Drugs that induce lupus **do not need to be avoided** in patients with idiopathic SLE unless they trigger symptoms.

Antiphospholipid syndrome (APS)

Overview

- APS is an **acquired autoimmune disorder** associated with **venous and arterial thrombosis**, **recurrent fetal loss**, and **thrombocytopenia**.
- It can occur as **primary APS** or **secondary to systemic lupus erythematosus (SLE)** or other autoimmune/lymphoproliferative disorders.
- A key feature is a **paradoxical rise in aPTT**, caused by lupus anticoagulant antibodies interfering with the coagulation cascade ex vivo.

Clinical Features

- **Thrombosis**: Both venous (e.g., deep vein thrombosis) and arterial (e.g., stroke).
- **Pregnancy complications**: Recurrent miscarriage, intrauterine growth restriction (IUGR), pre-eclampsia, placental abruption, preterm delivery.
- **Other features**:
  - **Livedo reticularis**.
  - **Prolonged aPTT** that does not correct with 50:50 mixing with normal plasma.
  - **Pulmonary hypertension**.
  - **False-positive VDRL** test.

Diagnosis

APS can be diagnosed if the following criteria are met:

1. **Antibodies** (on two occasions, 12 weeks apart):
   - Lupus anticoagulant.
   - Anti-beta-2 glycoprotein I antibodies.
   - Anticardiolipin antibodies.
2. **Clinical Criteria**:
   - A history of **thrombotic events**.
   - **Recurrent pregnancy loss**:
     - ≥3 consecutive losses before 10 weeks.
     - 1 loss after 10 weeks without other causes.

Management (Based on BCSH Guidelines)

1. **Initial Venous Thromboembolism (VTE)**:
   - **Warfarin**: Target INR of 2-3 for **6 months**.
   - **Lifelong anticoagulation** may be recommended, as recurrence risk is 20-70%.
2. **Recurrent VTE**:
   - Lifelong **warfarin,** with the target INR increased to **3-4** if thrombosis occurs while on warfarin.
3. **Arterial Thrombosis**:
   - Lifelong **warfarin** with a target INR of **2-3**.
4. **Pregnancy Management**:
   - **Low-dose aspirin**: Started upon pregnancy confirmation.
   - **Low molecular weight heparin (LMWH)**: Initiated when a fetal heartbeat is detected, discontinued at **34 weeks**.
   - These interventions **increase live birth rates** significantly.

Differential Diagnosis for Prolonged aPTT

1. **Coagulation factor deficiency**: e.g., Factor VIII or IX deficiency, von Willebrand disease.
2. **Factor VIII inhibitor**: Time-dependent effect—initial correction in 50:50 mix but no correction after incubation.

3. **Lupus anticoagulant (LAC):**
   - Prolonged phospholipid-dependent coagulation test (e.g., aPTT).
   - Lack of correction with normal plasma (50:50 mixing studies).
   - Correction with added phospholipid confirms phospholipid dependence.

Prognosis and Key Points

- **Spontaneous recovery** occurs with withdrawal of the offending drug in drug-induced cases.
- Lupus anticoagulant is the **strongest predictor** of thrombosis.
- In **pregnancy**, managing APS with aspirin and LMWH significantly reduces fetal loss and improves outcomes.

Juvenile Idiopathic Arthritis (JIA) / Still's Disease

Definition

- Juvenile idiopathic arthritis (JIA) is defined by **onset before 16 years of age** with **symptoms persisting for at least 6 weeks**.

Epidemiology

- **Most common arthritis** in children and adolescents.
- Prevalence: **1/1000 children.**
- **Sex ratio**: Females > Males.

Types of JIA

Type	Features	Treatment
Oligoarticular JIA	- Most common (50% of cases). - Affects **≤ 4 joints** in the first 6 months. - **High risk of anterior uveitis** (25%). - ANA positive (70%).	NSAIDs, intra-articular steroids, methotrexate
Polyarticular JIA	- Involves **≥ 5 joints**. - Accounts for 40% of cases. - ANA positive (40%), RF negative.	NSAIDs, methotrexate.
Systemic-onset JIA (Still's Disease)	- <10% of cases. - Presents with **fever, rash, hepatosplenomegaly, lymphadenopathy, serositis**. - RF negative, ↑ CRP, ferritin.	Methotrexate, IL-6 inhibitors, TNF inhibitors (e.g., etanercept, adalimumab).

Risk Factors

- **Antibiotic exposure** during childhood may increase the risk of JIA.

Clinical Features

- **Joint Pain**: Persistent swelling, especially in large joints.
- **Daily spiking fevers** and a **salmon-pink rash**.
- **Anterior uveitis**: Common, especially in ANA-positive cases (30-50%); asymptomatic at onset, requiring regular slit-lamp examination.
  - Complications of untreated uveitis: Cataracts, glaucoma, and macular edema.
  - If uveitis persists despite methotrexate, **adalimumab** is preferred over etanercept.
- **Systemic involvement**: Microcytic anemia, pericarditis, hepatosplenomegaly, osteoporosis.
- **ESR elevated** in most cases; RF and rheumatoid nodules are generally absent.

Diagnosis

- **Positive ANA**: Common (especially in oligoarticular JIA).
- **RF negative** except in **seropositive polyarticular JIA**.
- **Screening for uveitis**: Essential to prevent complications.

Management

- **First-line**: NSAIDs, corticosteroids.
- **Methotrexate**: Standard for moderate-to-severe cases.
- **Biologics** (TNF inhibitors and IL-6 receptor antibodies):
    - Used if **methotrexate fails**.
    - Examples: **Adalimumab, etanercept, tocilizumab**.
- **NICE guidance**: Recommends biologic therapy if methotrexate is ineffective.

Prognosis

- **Anti-CCP antibodies**: Indicator of poor prognosis.
- **Early onset**: Associated with higher risk of **growth impairment** and **joint deformities**.

Adult-Onset Still's Disease (AOSD)

Aspect	Details
Definition	A rare **systemic inflammatory disorder** characterized by recurrent **fever, arthritis**, and **rash**.
Epidemiology	- Affects **adults** (usually 16-35 years old). - Equal prevalence in males and females.
Etiology and Pathogenesis	- Unknown cause; potential involvement of **genetic predisposition** and **immune dysregulation**. - High levels of **cytokines** (IL-1, IL-6, and IL-18) are observed.
Clinical Features	- **High spiking fever** (>39°C), often occurring in the evening. - **Salmon-pink rash**: Non-pruritic, seen on the trunk and extremities during fever spikes. - **Polyarthritis**: Usually symmetrical, involving large joints. - **Sore throat** at disease onset. - Systemic features: **Lymphadenopathy, hepatosplenomegaly, pleuritis**, and **pericarditis**.
Laboratory Findings	- **Elevated inflammatory markers**: ESR, CRP, and ferritin (can be extremely high). - **Leukocytosis**: Often with neutrophilia. - Negative ANA and RF (useful to differentiate from autoimmune diseases).
Complications	- **Macrophage activation syndrome (MAS)**: Life-threatening complication with multi-organ failure. - **Chronic arthritis** and **joint damage**.
Diagnosis	- Based on **clinical features** and **exclusion of other causes** (e.g., infections, malignancies, autoimmune diseases). - **Yamaguchi criteria**: Requires fever, arthritis, rash, and leukocytosis along with other systemic features.

Aspect	Details
Management	- **NSAIDs**: First-line for mild disease to reduce fever and joint symptoms. - **Corticosteroids**: Prednisolone (0.5–1 mg/kg/day) for moderate-to-severe disease. - **Methotrexate**: Used for steroid-sparing and chronic arthritis. - **Biologic agents**: IL-1 inhibitors (e.g., anakinra) and IL-6 inhibitors (e.g., tocilizumab) for refractory disease.
Prognosis	- Variable course: Some patients experience **self-limiting disease**, while others develop **chronic arthritis**. - **Early treatment** improves outcomes and reduces the risk of complications.

Raynaud's Phenomenon

Definition

- **Raynaud's phenomenon** is characterized by **recurrent vasospasms** of the fingers and toes, often triggered by **cold exposure or stress**.

Types of Raynaud's Phenomenon

1. **Primary Raynaud's Phenomenon (Raynaud Disease)**
   - Occurs **without an underlying illness**.
   - **Common in young women** (~30 years old) with **symmetrical attacks**.
   - **Diagnosis criteria**:
     - Episodes triggered by cold/stress.
     - No signs of underlying disease.
     - Symmetrical involvement of both hands.
     - No tissue necrosis, ulcers, or severe ischemia.
     - **Normal nail-fold capillaries**, ESR, and negative ANA.
2. **Secondary Raynaud's Phenomenon**
   - **Secondary causes**:
     - **Connective tissue diseases** (e.g., scleroderma, rheumatoid arthritis, SLE).
     - **Hematologic disorders** (e.g., leukemia, polycythemia, cryoglobulinemia).
     - **Drug-induced**: Beta-blockers, oral contraceptives, ergot derivatives.
     - **Other**: Vasculitides, vibrating tools, cervical rib.
   - **Features suggesting underlying disease**:
     - Onset **after 40 years**.
     - Longer episodes (>1 hour).
     - Unilateral symptoms, rashes, or autoantibodies.
     - Digital ulcers, calcinosis, or rare occurrences like chilblains.

Investigations

- **Nail-fold capillaroscopy**:
  - Helps distinguish **primary from secondary Raynaud's**.
  - **Procedure**: A drop of oil applied to the periungual area, examined with an ophthalmoscope.
  - **Findings** in connective tissue disease (e.g., systemic sclerosis): Dilated, distorted, or absent capillary loops.

Management

1. **Primary Raynaud's Phenomenon**
   - **First-line**: Lifestyle measures.
     - Heated gloves, smoking cessation, and avoiding cold environments.
   - **Second-line**: Pharmacological treatment.
     - **Calcium channel blockers** (e.g., nifedipine).
     - **IV prostacyclin infusions** (e.g., iloprost) for non-responsive cases or digital ulcers.
     - **Urgent cases**: Intravenous iloprost for threatened gangrene.
   - **Third-line**: Non-pharmacologic treatment.
     - **Digital sympathectomy** as a last resort when medications fail.
2. **Secondary Raynaud's Phenomenon**
   - **Treatment focuses on managing the underlying disorder**.
   - **ACE inhibitors** offer **reno-protection** in autoimmune-related cases but are **not beneficial** without autoimmune pathology.
   - **Antiplatelet agents** have been trialled but show no definitive benefit.

Raynaud's Phenomenon: Primary vs. Secondary

Aspect	Primary Raynaud's Phenomenon (Raynaud Disease)	Secondary Raynaud's Phenomenon
Definition	Occurs **without an underlying disease**.	Associated with **underlying conditions** (e.g., autoimmune diseases).
Age of Onset	Typically affects **young women** (~30 years old).	Onset often **after 40 years**.
Symmetry	**Symmetrical** involvement of both hands.	Can present with **unilateral** symptoms.
Triggers	**Cold exposure** or **stress**.	Same triggers, but **episodes last longer** (>1 hour).
Nail-Fold Capillaroscopy	**Normal** capillary findings.	**Abnormal** capillaries: dilated, distorted, or absent loops (seen in connective tissue disorders).
Associated Symptoms	No ulcers, gangrene, or tissue necrosis.	May present with **digital ulcers**, **calcinosis**, and **chilblains** (rare).
Systemic Associations	None.	**Connective tissue diseases** (e.g., scleroderma, SLE, rheumatoid arthritis). Also associated with hematologic and drug-induced causes.
Laboratory Findings	**Normal ESR**, negative ANA.	**Positive autoantibodies** (e.g., ANA).
Management	Lifestyle changes (e.g., heated gloves), **nifedipine** as first-line drug.	**Treat underlying disorder**, ACE inhibitors if autoimmune disease present.
Prognosis	Generally **benign** and manageable with lifestyle changes.	Prognosis depends on the severity of the underlying disease.

Systemic sclerosis (Scleroderma)

Definition and Pathogenesis

- Systemic sclerosis (SSc) is a **chronic autoimmune disease** characterized by **fibrosis** of the skin and internal organs, **vascular abnormalities**, and immune dysregulation. High levels of **cytokines** such as IL-6 and TGF-beta play a role in fibrosis progression.

Types

1. **Limited Cutaneous SSc**: Affects hands, face, and forearms; associated with pulmonary hypertension.
2. **Diffuse Cutaneous SSc**: Involves widespread skin and internal organs, with a higher risk of lung and kidney involvement.

Clinical Features

- **Skin**: Thickening and tightening.
- **Raynaud's phenomenon**: Often the first sign.
- **Organ involvement**: Interstitial lung disease (ILD), pulmonary arterial hypertension, renal crisis, and gastrointestinal dysfunction.

Complications

- **Pulmonary hypertension** and **interstitial lung disease** are major causes of morbidity.
- **Renal crisis**: Often linked to uncontrolled hypertension.

Diagnosis

- **Autoantibodies**: Anti-centromere (limited SSc) and anti-Scl-70 (diffuse SSc).
- **Imaging**: HRCT for lung involvement, echocardiography for pulmonary hypertension.

Management

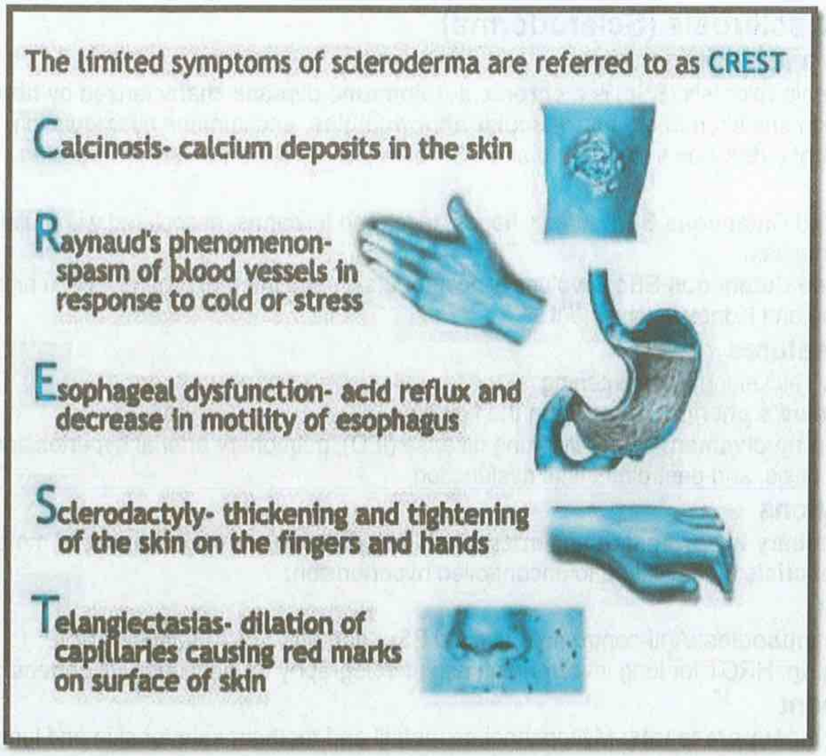
- **Immunosuppressants**: Mycophenolate mofetil and methotrexate for skin and lung involvement.
- **Antifibrotic agent**: Nintedanib for progressive ILD.
- **Biologics**: Tocilizumab and rituximab in refractory cases.
- **Vasodilators**: PDE5 inhibitors or endothelin receptor antagonists (e.g., bosentan) for pulmonary hypertension.

Prognosis and Monitoring

- **Frequent follow-ups** every 3-6 months to monitor treatment efficacy.
- **Early intervention** improves outcomes, especially for ILD and pulmonary hypertension.

Comparison of Limited vs. Diffuse Cutaneous Systemic Sclerosis (SSc)

Aspect	Limited Cutaneous SSc	Diffuse Cutaneous SSc
Skin Involvement	Confined to **hands, face, forearms**.	Widespread, involving **trunk and proximal limbs**.
Onset	**Gradual** onset of symptoms.	**Rapid** progression of skin thickening.
Organ Involvement	Associated with **pulmonary hypertension**.	Increased risk of **interstitial lung disease (ILD)** and **renal crisis**.
Autoantibodies	**Anti-centromere** antibodies common.	**Anti-Scl-70** antibodies more frequent.
Prognosis	Generally **better** with slower progression.	More **severe** with higher morbidity.



Polymyalgia rheumatica (PMR)

Pathophysiology

- **Overlap with giant cell arteritis (GCA)**: 30% of patients with PMR may also develop GCA.
- Involves **vasculitis of muscle bed arteries**, but without direct muscle damage.

Epidemiology

- Affects **people over 50 years**, more common in **women**.

Clinical Features

- **Rapid onset** of pain and stiffness in **shoulders and hips**.
- **Morning stiffness**, fatigue, low-grade fever, weight loss, and mild depression.

Diagnosis

- **Elevated ESR (>40 mm/hr)** and **CRP**.
- **Normal CK and EMG** findings.
- **Normocytic anemia** may be present.

Treatment

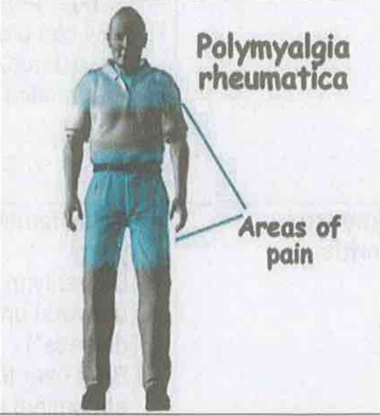
- **Prednisolone**: Initial dose of **15 mg/day**, with improvement within 24-72 hours.
- **Calcium and vitamin D** supplements are essential, and **bisphosphonates** for long-term steroid use.
- **Tapering**: Reduce dose gradually based on symptom control.
- **Methotrexate or azathioprine**: Used as **steroid-sparing agents** for prolonged treatment or steroid intolerance.

Prognosis

- **Rapid symptom relief** often occurs within 24-72 hours with proper treatment.
- Many patients can discontinue steroids within **2 years** of treatment.

Polymyalgia rheumatica (PMR)

- Age > 60 years old (very rarely seen in the under 50s).
- Rapid onset (e.g. < 1 month)
- **Pain and stiffness of the shoulder and pelvic girdle muscles,** worst in the mornings
- Mild polyarthralgia, lethargy,
- Depression
- **Low-grade fever**, anorexia, night sweats
- **Weight loss**



Patients with polymyalgia rheumatica (PMR) should respond completely to 20 mg daily of prednisone and normalize their erythrocyte sedimentation rate (ESR) within a month. (The presence of fever or failure to respond to prednisone clinically and serologically suggests giant cell arteritis)

(GCA) or another diagnosis such as lymphoma.)

- **Prednisolone** e.g. 15mg/od - dramatic response
  - ⇨ Response to a moderate dose of steroids can be useful in confirming the diagnosis of PMR.
  - ⇨ The maximum dose of prednisolone should not exceed 20 mg once daily.
  - ⇨ Patients should report 70% improvement in symptoms within three to four weeks, and inflammatory markers should have normalised by this point.

Differential diagnosis of vasculitis

After ruling out infection and malignancy, consider vasculitis in any patient with multisystem disease who has an ESR >100 mm/hour and a C-reactive protein >10 times the upper limit of normal.

The primary vasculitides (i.e., vasculitis not due to another disease such as SLE or cryoglobulinemia) are not associated with positive serologies (ANA, RF, low complements), neutropenia, or thrombocytopenia. If one of these is present, consider another diagnosis.

	Clinical presentation	Diagnostic clues
Giant cell arteritis	▪ Age, typically > 50 years ▪ ↓Vision → blindness. ▪ New-onset headache ▪ Tender temporal artery ▪ Jaw claudication ▪ Associated with polymyalgia rheumatica	▪ ↑ ESR ▪ Autoantibodies absent ▪ Halo sign around the vessel on duplex sonography ▪ Temporal artery biopsy (gold standard) shows granulomatous inflammation with giant cells and intima proliferation that results in stenosis.
Takayasu arteritis	▪ Asian females, typically < 40 years ▪ Disparity in blood pressure between arms ("pulseless disease") ▪ Bruit over the subclavian artery or abdominal aorta ▪ Syncope and angina pectoris	▪ ↑ ESR ▪ Angiography shows stenosis of aortic arch and proximal great vessels (gold standard). ▪ Biopsy shows granulomatous inflammation of the aorta and its major branches.
Kawasaki syndrome	▪ Children < 5 years ▪ "CRASH (Conjunctivitis, Rash, Adenopathy, Strawberry tongue, Hand-foot changes) and BURN (≥ 5 days of fever)	▪ ↑ ESR, ↑ CRP, thrombocytosis ▪ Echocardiography may detect coronary artery aneurysms.
Polyarteritis nodosa	▪ 45–65 years, ♂ > ♀ ▪ Fever, malaise ▪ Abdominal, muscle, and joint pain ▪ Renal impairment ▪ Neurologic dysfunction (e.g., polyneuropathy, stroke) ▪ Rash, ulcerations, nodules	▪ Association with hepatitis B and hepatitis C ▪ Spares the lungs ▪ ANCA-negative ▪ Muscle biopsy shows transmural inflammation of vessels.
Thromboangiitis obliterans (Buerger disease)	▪ Men < 45 years ▪ Strong association with tobacco use ▪ Intermittent claudication due to severe limb ischemia; acute necrosis of toes and fingers often requires amputation. ▪ Raynaud phenomenon	▪ Angiography (confirmatory test): nonatherosclerotic segmental occlusion of arteries

	Clinical presentation	Diagnostic clues
Granulomatosis with polyangiitis (Wegener)	▪ 35–55 years; ♂ > ♀ ▪ Nasopharyngeal involvement: chronic sinusitis/rhinitis, saddle nose deformity ▪ Chronic otitis media and mastoiditis ▪ Treatment-resistant, pneumonia-like symptoms with cough, dyspnoea, haemoptysis ▪ Rapid progressive glomerulonephritis	▪ PR3-ANCA/cANCA-associated ▪ Biopsy shows granulomatous, necrotizing inflammation of vessels, kidneys, and the lungs. ▪ Chest x-ray/CT: multiple bilateral cavitating nodular lesions
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	▪ Severe allergic asthma, sinusitis ▪ Skin manifestations (e.g., tender nodules) ▪ Peripheral neuropathy ▪ Gastrointestinal, cardiac, renal involvement possible	▪ MPO-ANCA/p-ANCA-associated ▪ Peripheral blood eosinophilia ▪ ↑ IgE ▪ Biopsy (confirmatory test): tissue eosinophilia and necrotizing granulomas
Microscopic polyangiitis	▪ Hypertension and pauci-immune glomerulonephritis ▪ Palpable purpura	▪ MPO-ANCA/p-ANCA-associated ▪ Similar to granulomatosis with polyangiitis but spares the nasopharynx ▪ Biopsy shows inflammation; no granulomas
Henoch-Schonlein purpura	▪ Children; 90% < 10 years ▪ **Tetrad of: PARA (Purpura, Abdominal pain, Renal involvement (haematuria and proteinuria), Arthritis)**	▪ Often secondary to upper respiratory tract infections ▪ ↑ IgA in serum ▪ Biopsy: leukocytoclastic vasculitis with IgA and C3 immune complex deposition
Cryoglobulinaemic vasculitis	▪ Fatigue, Arthralgia ▪ Palpable purpura ▪ Glomerulonephritis	▪ The majority of cases are secondary to hepatitis C infection. ▪ Cryoglobulinemia
Behcet disease	▪ Most common in Turkey, the Middle East, and Japan ▪ Oral and genital ulcers ▪ Uveitis ▪ Erythema nodosum	▪ Positive pathergy skin testing

Temporal arteritis (Giant cell arteritis (GCA)

Definition

- GCA is a **large-vessel vasculitis** primarily affecting individuals over 50 years old. It often overlaps with **polymyalgia rheumatica (PMR)** and is considered a **medical emergency** due to its potential to cause **vision loss**.

Clinical Features

- **Headache** (85%), **jaw claudication** (65%), and **visual disturbances** (50%).
- **Tender temporal artery**, morning stiffness (PMR-like symptoms).
- Aortic aneurysm occurs in 10-20% of cases.

Diagnosis

- **Elevated ESR and CRP**; ESR >50 mm/hr in most cases.
- **Temporal artery biopsy**: Definitive but can yield false negatives due to **skip lesions**.

Treatment

- **High-dose prednisolone**: 40-60 mg/day for uncomplicated cases; IV methylprednisolone for visual symptoms.
- **Bone-sparing agents** and **aspirin** recommended to prevent complications.
- **Urgent ophthalmology referral** for visual symptoms, as damage may be irreversible.

GCA should always be considered in elderly patients with headaches, ocular symptoms (e.g. acute monocular visual loss), systemic symptoms and high ESR.

Suspected GCA → glucocorticoids immediately, even before diagnostic evaluation by temporal artery biopsy is complete.

GCA is the most common vasculitis in the elderly, and jaw claudication is the most specific symptom.

Listen for subclavian bruits in all patients suspected of having GCA as it may be their only clinical finding. Large vessel involvement puts them at increased (17×) risk for aortic dissections and aneurysms

Polyarteritis Nodosa (PAN)

Definition

- PAN is a **systemic necrotizing vasculitis** of **medium-sized vessels**, causing tissue ischemia and aneurysm formation. It can affect any organ except the **lungs**.

Epidemiology and Associations

- Affects **middle-aged men** (♂ > ♀).
- **Hepatitis B infection** is a known risk factor.

Clinical Features

- **Nonspecific symptoms**: Fever, malaise, weight loss, arthralgia.
- **Neurological**: Polyneuropathy, stroke.
- **Renal**: Hypertension, hematuria.
- **Skin**: Livedo reticularis, ulcers.
- **GI**: Abdominal pain, melena.
- **Testicular pain** from ischemia.

Diagnosis

- **Angiography**: Microaneurysms, vessel narrowing.
- **Biopsy**: Transmural necrosis without granulomas.
- **Negative ANCA**; positive hepatitis B antigen in 30%.

Treatment

- **Idiopathic PAN**: Corticosteroids and cyclophosphamide.
- **Hepatitis B-related PAN**: Plasmapheresis and antivirals.
- **Maintenance therapy**: Azathioprine preferred for fewer side effects.

Granulomatosis with polyangiitis (Wegener's granulomatosis)

Definition

- GPA is a **systemic vasculitis** affecting **small- and medium-sized vessels**, characterized by **necrotizing granulomatous inflammation**. It commonly involves the **upper respiratory tract, lungs, and kidneys**.

Clinical Features

- **ENT**: Sinusitis, nasal ulcers.
- **Lungs**: Hemoptysis, nodules, or cavitations.
- **Kidneys**: Glomerulonephritis, proteinuria, hematuria.
- **Systemic**: Fever, weight loss, arthralgia.

Diagnosis

- Positive **c-ANCA** (anti-PR3).
- **Biopsy**: Granulomas and vasculitis in affected tissues.

Treatment

- **Induction**: Steroids + **cyclophosphamide** or **rituximab**.
- **Maintenance**: Methotrexate or azathioprine.
- Early treatment prevents organ damage and improves prognosis.

The classical triad of Granulomatosis with polyangiitis;

1. Necrotising granulomatous inflammation of the upper/lower respiratory tract.
2. Glomerulonephritis.
3. small-vessel vasculitis.

	Granulomatosis with polyangiitis	Microscopic polyangiitis
Features	➲ Glomerulonephritis ➲ Localized necrotizing vasculitis ➲ Upper/lower respiratory tract manifestations with noncaseating, necrotizing granulomas	➲ Potentially palpable purpura ➲ Nasopharyngeal involvement less common ➲ No granulomatous inflammation
Antibodies	➲ PR3-ANCA/c-ANCA (anti-proteinase 3)	➲ MPO-ANCA/p-ANCA (anti-myeloperoxidase)

Microscopic polyangiitis is similar to Granulomatosis with polyangiitis (Wegener's granulomatosis) except in 3 things:

1. it only affects small blood vessels in the lungs or kidneys.(No nasopharyngeal damage like wegener's)
2. Associated more with anti-MPO (pANCA, 45%) than anti-PR3 (cANCA, 30%)
3. No granuloma on biopsy

PassOnExam

Microscopic polyangiitis should be considered in all patients presenting with pulmonary– renal syndrome and is associated with myeloperoxidase-ANCA.

Churg-Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis - EGPA)

Definition and Pathophysiology:

- EGPA is a rare systemic vasculitis involving small- to medium-sized blood vessels, characterized by asthma, eosinophilia, and organ damage.
- It progresses through three phases: allergic (asthma, rhinitis), eosinophilic (organ infiltration by eosinophils), and vasculitic (vascular inflammation and systemic symptoms).

Diagnostic Features:

- High eosinophil count (>10% of WBCs).
- Involvement of multiple organs (skin, lungs, kidneys, nerves, heart).
- Presence of antineutrophil cytoplasmic antibodies (ANCA) in some patients.

Treatment:

1. **Corticosteroids** – Prednisolone forms the backbone (initial high doses tapered over time).
2. **Cyclophosphamide** – For severe or refractory cases; used for induction.
3. **Azathioprine or Methotrexate** – Maintenance therapy after remission.
4. **Rituximab** – Reserved for refractory EGPA or ANCA-positive cases.
5. **Inhaled/Nasal Steroids** – To control asthma and sinus symptoms.

Churg-Strauss syndrome: pANCA and polyneuropathy (foot or wrist drop), allergic rhinitis/sinusitis/asthma, vasculitis, eosinophilia, and skin nodules

Leukotriene receptor antagonists may precipitate the disease

Henoch-Schonlein purpura (HSP)

Aspect	Details
Definition	IgA-mediated small vessel vasculitis affecting the skin, GI tract, kidneys, and joints.
Epidemiology	More common in **males** than females; **90%** of cases occur in children (<10 years old).
Pathophysiology	Allergen/antigen exposure → **IgA production** → IgA immune complex deposition → complement activation → vasculitis.
Predisposing Factors	- **Infections:** Viral or bacterial (e.g., group A Streptococcus) 1–3 weeks prior - **Drugs:** β-lactam antibiotics, vaccines - **IgA nephropathy** and **genetic predisposition** - Chronic alcohol use in adults.
Features	**Skin:** Palpable purpura on buttocks and extensor surfaces **Joints:** Arthritis, especially in knees/ankles **GI:** Abdominal pain, possible bloody diarrhoea **Kidneys:** IgA nephritis, haematuria, proteinuria (worse prognosis if nephrotic range proteinuria).
Tetrad (mnemonic: PARA)	**P**urpura, **A**bdominal pain, **R**enal involvement (haematuria/proteinuria), **A**rthritis
Diagnosis	**Skin biopsy + immunofluorescence:** Leukocytoclastic vasculitis with IgA deposits **(pathognomonic).**
Treatment	- **Mild cases:** Analgesia - **Severe cases:** IV methylprednisolone (glucocorticoids) - **Renal involvement:** ACE inhibitors for hypertension/proteinuria - **Adults:** Immunomodulatory therapy often required.
Prognosis	- Most cases resolve spontaneously, especially in children. - Relapses more likely in patients with renal involvement. - **Worse prognosis** in nephrotic-range proteinuria; **ESRD** may occur in 1% of cases.

The platelet count in Henoch-Schonlein purpura is normal or elevated, as opposed to other causes of purpura.

Henoch-Schonlein purpura (HSP) is the tetrad of:

1. **Purpura**
2. **Abdominal pain**
3. **Renal involvement (haematuria and proteinuria)**
4. **Arthritis**

Incidence: most common in children <17 years.

Mechanism: IgA mediated small vessel vasculitis.

Diagnosis: Skin biopsy → leukocytoclastic vasculitis with IgA deposits within blood vessel walls.

Treatment:

- **For pain: 1st line → naproxen. 2nd line → prednisone.**
- **for hypertension and proteinuria → ACE inhibitor.**

Prognosis: self-limited → Full renal recovery.

Kawasaki disease (KD)

Category	Details
Definition	A vasculitis of medium-sized arteries, particularly affecting children, which can lead to coronary artery complications if untreated.
Epidemiology	Most commonly affects children under 5 years old, with a higher incidence in East Asian populations.
Causes	The exact cause is unknown but likely involves an abnormal immune response to infections.
Clinical Features	Fever lasting ≥5 days and at least four of the following:
	- Bilateral non-exudative conjunctivitis
	- Oral mucositis (e.g., strawberry tongue, red cracked lips)
	- Cervical lymphadenopathy (≥1.5 cm, usually unilateral)
	- Polymorphous rash
	- Extremity changes (e.g., erythema or desquamation of palms/soles)
	Complications: Coronary artery aneurysms, myocarditis, arrhythmias
Investigations	- No specific diagnostic test
	- **Echocardiogram:** To detect coronary aneurysms
	- **Blood tests:** Elevated CRP, ESR, leukocytosis, thrombocytosis
	- **Urinalysis:** Sterile pyuria (common)
Diagnosis	Clinical diagnosis based on symptoms and exclusion of other febrile illnesses.
Treatment	**Acute Phase:**
	- Intravenous Immunoglobulin (IVIG) 2 g/kg (single dose)
	- High-dose aspirin (30-50 mg/kg/day, divided) to reduce inflammation
	Maintenance:
	- Low-dose aspirin (3-5 mg/kg/day) for 6-8 weeks to prevent thrombosis
Monitoring	- Regular echocardiograms to monitor coronary artery involvement
Prognosis	Good if treated early with IVIG; untreated KD can lead to coronary aneurysms and long-term cardiovascular issues.

Consider Kawasaki disease in any child aged <5 years presenting with prolonged high fevers and conjunctivitis.

Intravenous immunoglobulin within 10 days of disease onset is the treatment of choice.

Takayasu's arteritis

Aspect	Details
Definition	Granulomatous inflammation of the aorta and its major branches, causing vessel thickening, stenosis, and vascular symptoms. Often affects the subclavian artery, leading to subclavian steal syndrome.
Pathology	Progressive inflammation with macrophages, lymphocytes, and multinucleated giant cells, resulting in occlusion of large arteries.
Epidemiology	Primarily affects young women (8:1 female-to-male ratio), with onset typically between 25–30 years. Most common in Asian populations.
Features	**General:** Fever, malaise, night sweats, arthralgia. **Vascular:** Absent or decreased brachial/radial pulses ("pulseless disease"), BP difference >10 mm Hg between arms, bilateral carotid bruits, hypertension, syncope, angina, claudication, Raynaud phenomenon, aortic regurgitation, and impaired vision. **Skin:** Erythema nodosum.
Investigations	**ESR and CRP:** Typically elevated. **Angiography (gold standard):** Shows vascular stenosis. **Biopsy:** Granulomatous thickening of the aortic arch.
Associations	Renal artery stenosis.
Treatment	**First-line:** Corticosteroids. **If refractory:** Methotrexate or cyclophosphamide.

Buerger's disease (Thromboangiitis obliterans)

Overview

- Thromboangiitis obliterans (Buerger's disease) is a disease of small and medium-sized arteries and veins resulting in inflammation and ulceration, in which the distal vessels become blocked in the hands and feet.

Definition

- An inflammatory, nonatherosclerotic vasculitic disease that affects both small and medium-sized arteries and veins, resulting in thrombotic occlusion of the distal vessels in hands and feet.

Epidemiology

- Prevalence is higher in men : ♂ > ♀ (3:1)
- **Age of onset**: before the age of 45 years

Pathophysiology

- **Inflammation of the tunica intima with neutrophilic infiltration and microabscess formation (endarteritis)** → inflammation may also spread to the tunica media but the internal elastic lamina usually remains intact. Unlike in other forms of vasculitis, the rest

of the vessel wall is usually relatively spared → development of cell-rich, inflammatory thrombi in the lumen → occlusion of the vessel.

- There is no excessive atheroma and it does not involve the coronary arteries like atherosclerosis.
- There is no systemic vasculitis , no elevation in acute phase markers and does not respond to immune suppression.

Risk factor

- **Smoking is the single most important risk factor (it has not been documented in non-smokers)**

Feature

- Superficial migratory thrombophlebitis with tender nodules along the course of the vein
- Symptoms of arterial ischaemia → resulting in **gangrene of the digits** (Digits may autoamputate)
  - ⇨ Intermittent claudication
  - ⇨ Cool peripheral extremities
  - ⇨ The feet or legs may be cyanosed or dusky; the skin is thin and without hair.
  - ⇨ Ulcerations occur, and necrosis follows

Diagnosis

- Usually clinical
- **Autoantibodies (e.g., ANA, RF) are absent and a hypercoagulability screen is normal.**
- **Ankle-brachial index** (ratio of systolic ankle BP to systolic brachial BP): decreased → peripheral arterial disease
- **Arteriogram** will show occlusion of distal arteries of the hands and feet.
- **Histopathology** of affected arteries reveals fresh inflammatory thrombus within both small and medium-sized arteries and veins, with giant cells surrounding the thrombus.

Treatment

- **Stop smoking: the single most important therapeutic measure**
- Medical therapy: Vasodilators
  - ⇨ Iloprost (prostacyclin analog)
  - ⇨ Calcium channel blockers (nifedipine, amlodipine)

Prognosis

- Can be excellent (i.e. complete resolution of symptoms) with smoking cessation
- In some cases, however, amputation is unavoidable

Buerger's disease

Idiopathic pulmonary hemosiderosis

Definition: recurrent episodes of diffuse alveolar hemorrhage of unknown aetiology
Prevalence: rare, tends to occur in younger people

Features

- Pallor
- Weakness, lethargy
- Dry cough and occasional haemoptysis
- **No extrapulmonary features**
- After recurrent episodes of hemorrhage, pulmonary fibrosis may develop due to iron accumulation.

Investigations

- **no abnormal immunological features, which differentiates it from Goodpasture syndrome and wegener's**
- Gas transfer is elevated as blood is already in the alveolar space.
- chest radiograph and high resolution computed tomography demonstrate ground glass alveolar opacities that are often bilateral.
- final diagnosis requires lung biopsy documentation of large numbers of hemosiderin-laden macrophages in the alveoli, without evidence of vasculitis, capillaritis, inflammation, granulomas, or deposition of immunoglobulins in any specific pattern.

Treatment

- glucocorticoids +/- another immunosuppressive agent (eg, azathioprine, or cyclophosphamide)

> ➧ **pulmonary hemorrhage <u>without immunological features</u> → Idiopathic pulmonary haemosiderosis**
> ➧ **pulmonary hemorrhage + immunological features → Goodpasture or wegener's**

Polyarthritis

Polyarthritis

Definition:

- Polyarthritis refers to **inflammation or pain affecting five or more joints**. It can result from various **inflammatory** and **non-inflammatory** conditions.

Differential Diagnosis of Polyarthritis

Inflammatory Causes	Non-inflammatory Causes
Rheumatoid arthritis (RA)	Osteoarthritis
Juvenile idiopathic arthritis	Chronic calcium pyrophosphate deposition disease (CPPD)
Sarcoid arthritis	Fibromyalgia
Systemic lupus erythematosus (SLE)	Hemochromatosis
Reactive arthritis	Benign hypermobility syndrome
Psoriatic arthritis	
Polyarticular gout	
Infectious arthritis (e.g., gonococcal, hepatitis B/C, HIV)	
Vasculitis	

Polyarthritis with Elevated ANA Titer (≥1:320)

- **Systemic lupus erythematosus (SLE)** (including drug-induced lupus)
- **Rheumatoid arthritis (RA)**
- **Sjögren's syndrome**
- **Polymyositis**
- **Systemic sclerosis**
- **Mixed connective tissue disease**

Polyarthritis with Raynaud's Phenomenon

- **Mixed connective tissue disease** (>90% prevalence)
- **Systemic sclerosis** (>90% prevalence)
- **Systemic lupus erythematosus (SLE)** (20% prevalence)
- **Polymyositis/Dermatomyositis** (20–40% prevalence)
- **Vasculitis**

Arthropathies Associated with Iron Deposition (Brown-Stained Synovial Fluid)

- **Haemophilia**
- **Hemosiderosis** from recurrent hemarthrosis
- **Haemochromatosis**
- **Pigmented villonodular synovitis (PVNS)**

Chronic polyarticular diseases associated with low serum complement levels (C3 and C4):

Disease	Low C3	Low C4	Mechanism
Systemic Lupus Erythematosus (SLE)	Yes	Yes	Immune complex formation depletes complement, especially in lupus nephritis.
Mixed Connective Tissue Disease (MCTD)	Sometimes	Yes	Complement consumption during severe or active disease phases.
Cryoglobulinaemia (Mixed Types II and III)	No	Yes	Classical pathway activation due to immune complexes, often with Hepatitis C.
Infective Endocarditis	Yes	Yes	Immune complex formation leads to complement consumption.

Myopathies

Polymyositis

Definition

- Inflammatory disorder causing **symmetrical**, **proximal**, **painless** muscle weakness

Pathophysiology

- thought to be a T-cell mediated cytotoxic process directed against muscle fibres

Epidemiology

- Typically affects middle-aged
- Female: male 3:1

Associated conditions

- Connective tissue disorders
- Interstitial lung disease → evaluate with chest x-ray and pulmonary function tests.
- Malignancy , commonly **Adenocarcinomas** , stronger for dermatomyositis, than for polymyositis. **The most appropriate next investigation → CT chest, abdomen and pelvis**

Features

- **Proximal muscle weakness** +/- tenderness
- Raynaud's
- **Mechanics hands** found in a subtype of polymyositis called anti-synthetase syndrome or Jo-1 syndrome →**fissuring and cracking on the distal digital pads of several fingers.**
- Respiratory muscle weakness
- **Interstitial lung disease**: e.g. fibrosing alveolitis or organising pneumonia
- **Dysphagia**, dysphonia

Investigations

- **Elevated creatine kinase (the initial investigation)**
- Electromyography (EMG): abnormal in almost all patients (90%).
  - ⇨ Triad of:
    1. Short, small polyphasia motor units
    2. Fibrillation and sharp waves
    3. Bizarre, repetitive discharges
- Muscle biopsy
  - ⇨ **the definitive investigation to establish the diagnosis**
  - ⇨ Histopathology → **endomysial** mononuclear **inflammatory infiltrate with CD8 T cells (MHC class I)** and muscle fiber **necrosis.**
- Anti-Jo-1 antibodies
  - ⇨ seen in pattern of disease associated with lung involvement, Raynaud's and fever
- **Antinuclear antibody** - Positive in one third

Treatment

- Prednisolone is the mainstay of treatment, at an initial dose of 1 mg/kg/d.
- In patients who fail to show improvement, disease-modifying steroid-sparing agents may be added.
- A high-protein diet and supervised exercise may further improve symptoms.

Prognosis

- Most patients have a favourable response to corticosteroid therapy, and 5-year survival rates approach 80%.

Dermatomyositis

Definition

- Dermatomyositis is a variant of an inflammatory myositis causing symmetrical, proximal muscle weakness and characteristic skin lesions, for example a purple **Heliotrope rash** on the cheeks and eyelids or **Gottron's papules**: roughened red papules over extensor surfaces of fingers

Pathophysiology

- **Autoantibodies binding to the vasculature**, muscle atrophy, and lymphocytic inflammation
- **caused by CD4 T cells that cause perimysial inflammation and atrophy.**

Features

- **Features of polymyositis** (proximal muscle weakness, Raynaud's, respiratory muscle weakness, interstitial lung disease, dysphagia, dysphonia)
- **Pathognomonic skin features**
  - ⇨ **Heliotrope rash** in the periorbital region
    - a violaceous or erythematous rash in a symmetrical distribution involving periorbital skin.
    - its presence is highly suggestive of dermatomyositis.
  - ⇨ **Gottron's papules**: roughened red papules over extensor surfaces of fingers
- Other skin lesions
  - ⇨ Photodistributed erythema, poikiloderma, nail fold changes
  - ⇨ **Mechanic's hands:** (rough, cracked skin)
  - ⇨ **Fingers telangiectasia:** Nail fold capillary dilatation.

- ⇨ **Shawl sign**: a macular rash over the back and shoulder
- ⇨ **V-neck sig:** Violaceous erythema or poikiloderma involving the anterior chest
- ↑↑↑ **risk of malignancy**

Associated features

- Malignancies (**dermatomycotic increases the risk of malignancy more than polymyositis**). typically lung cancer, found in 20-25%
- Interstitial lung disease (ILD) occurs in at least 10%

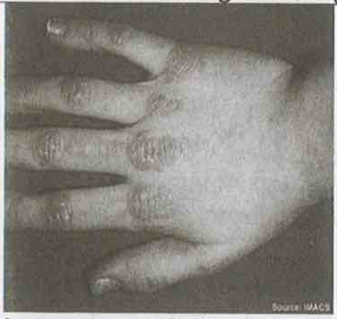


Image shows: Gottron's papules

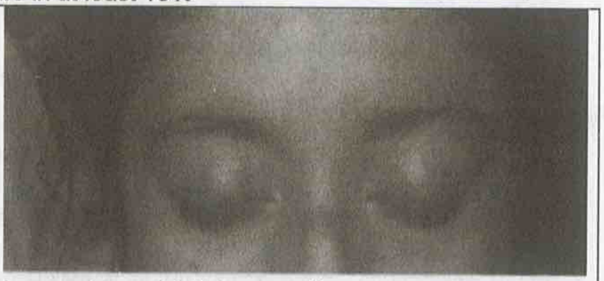


Image shows: Heliotrope rash

Investigations

- Elevated creatine kinase → **the most helpful initial test**
- EMG
- Muscle biopsy
  - ⇨ high levels of the complement component **C5b-9 around the capillary vessels.**
  - ⇨ **Perimysial inflammation with lymphocytic infiltrate**
- ANA positive in 60%
- **Anti-Mi-2 antibodies are highly specific** for dermatomyositis but are only seen in around 25% of patients
- **Screen for malignancy**

Management

- Prednisolone
- Glucocorticoid-sparing agents: azathioprine or methotrexate.

Prognosis

- Relatively good, with **most patients reaching remission after 2–3 years**, except of course where there is an associated underlying malignancy.

Proximal weakness with normal reflexes and sensation and absence of fasciculations:
- **without skin lesion → polymyositis**
- **with skin lesion → dermatomyositis**

Dermatomyositis antibodies: ANA most common, anti-Mi-2 most specific

Inclusion body myositis (IBM)

Definition

- a syndrome of diffuse, progressive, **asymmetric**, proximal, and distal weakness that is generally **refractory to immunosuppressive treatment**.
- The aetiology of IBM is largely unknown.

Epidemiology

- IBM occurs **more frequently in men than women**.
- More common in older Caucasian males.
- the most common acquired myopathy in **patients older than 50 years**

Features

- Muscle weakness can affect **both proximal and distal muscles**
  - ⇨ **unlike polymyositis and dermatomyositis, asymmetry is common.**
  - ⇨ characteristically early affects quadriceps and finger/wrist flexors are usually more severely
  - ⇨ The onset of muscle weakness in IBM is generally gradual (over months or years).
- Dysphagia is common, occurring in 40-66% of patients
- Difficulties with breathing →the most common cause of death is respiratory system disorders.

Diagnosis

- creatine kinase (CK) levels: no striking elevation (less than 10 times normal).
- anti-**cN1A** autoantibodies
- Muscle biopsy
  - ⇨ shows **intranuclear or cytoplasmic tubofilaments** on electron microscopy.
  - ⇨ The specific finding is the presence of **sarcoplasmic "rimmed" vacuoles**

Treatment

- Optimal treatment for IBM is not known
- Unlike dermatomyositis and polymyositis, IBM is relatively resistant to standard immunomodulatory therapies.

	Polymyositis	Dermatomyositis	IBM
Onset	Subacute	Subacute	Slow
Age	Commonest < 50 years	Commonest < 50 years	Commonest > 50 years
Affected muscles	Proximal	Proximal	Proximal and distal
symmetry	Symmetrical	Symmetrical	Asymmetrical
Common incidence	Female	Female	Male
Skin lesion	NO	Characteristic rash	NO
CK	Highly elevated (up to 50 fold)	Highly elevated (up to 50 fold)	Mild elevated (up to 10 fold) or normal
Antibodies	anti-Jo-1 are more common	Anti-Mi-2 are highly specific	Anti-cN1A autoantibodies

Category	Types / Causes	Diagnostic Features	Treatment
Paraneoplastic Myopathy	- Associated with cancers (lung, GIT, breast, kidney, prostate)	- Weakness, muscle atrophy - Resistant to glucocorticoids - Diagnosis confirmed by cancer screening	Treatment of the underlying cancer.
Infectious Myopathies	- Viral infections (e.g., influenza, HIV) - Bacterial infections - Metabolic disorders	- **Acute weakness** with cramps, rhabdomyolysis, myoglobinuria - CK mildly elevated in HIV polymyositis	**Glucocorticoids**, azathioprine, IVIg in HIV polymyositis
Drugs- and Toxin-induced Myopathies	- Cholesterol-lowering drugs (statins) - Alcohol, amphetamines, heroin, cocaine - Other drugs: d-Penicillamine, steroids, chloroquine, vincristine	- Rhabdomyolysis and myoglobinuria - Inflammatory or non-inflammatory types identified by clinical and biopsy findings	Discontinue offending drug; supportive care.
Critical Illness Myopathy (CIM)	- Associated with sepsis, organ failure, or prolonged ICU stay	- Weakness, difficulty weaning off ventilators - Mildly elevated CK - Muscle biopsy required to differentiate from other causes	Avoid corticosteroids and neuromuscular blocking agents.
Metabolic Myopathies	- Vitamin D deficiency - Hypokalemia or hyperkalemia - Hypophosphatemia	- Weakness, cramps, and **exercise intolerance** - Vitamin D deficiency causes **proximal myopathy** and osteomalacia	Correct underlying metabolic abnormalities (e.g., potassium, phosphate).

Category	Types / Causes	Diagnostic Features	Treatment
Inherited Metabolic Myopathies	- Glycogen storage diseases - Lipid storage myopathies - Mitochondrial diseases	- **Glycogen storage disease**: Elevated CK at rest, PAS-positive granules on biopsy - **Lipid storage myopathies**: Carnitine deficiency, CPT2 deficiency - **Mitochondrial myopathy**: Lactic acidosis, ragged red fibers on biopsy	**Enzyme replacement** for glycogen storage diseases Supportive care for mitochondrial myopa

Inflammatory Back Pain

Category	Details
Definition	Chronic back pain caused by **inflammatory conditions**, typically lasting **>3 months**, with improvement during physical activity and worsening with rest.
Criteria	- **Age of onset**: <40 years - **Insidious onset** - **Improves with exercise** - **No improvement with rest** - **Night pain** that improves on getting up
Causes	- **Ankylosing spondylitis** - **Psoriatic arthritis** - **Reactive arthritis** - **Enteropathic arthritis** (associated with inflammatory bowel disease) - **Non-radiographic axial spondyloarthritis**

Causes, Diagnostic Features, and Management

Cause	Specific Diagnostic Features	Management
Ankylosing Spondylitis	- **Sacroiliitis** on X-ray or MRI - **HLA-B27 positive** (in 90% of cases) - Limited spinal mobility - Elevated ESR/CRP	1. **NSAIDs** (first-line) 2. **TNF inhibitors** (e.g., infliximab, etanercept) for refractory cases 3. **Physiotherapy** and posture correction
Psoriatic Arthritis	- **Psoriasis** skin lesions (scalp, elbows) - **Dactylitis** ("sausage digits") - Enthesitis (inflammation at tendon insertions)	1. **NSAIDs** 2. **DMARDs** (e.g., methotrexate) 3. **TNF inhibitors** or **IL-17 inhibitors** (e.g., secukinumab) for severe cases

Cause	Specific Diagnostic Features	Management
Reactive Arthritis	- **History of infection** (e.g., Chlamydia, Salmonella) - **Asymmetric oligoarthritis** - Uveitis, conjunctivitis	1. **NSAIDs** 2. **Antibiotics** if active infection is present 3. **DMARDs** (e.g., sulfasalazine) for chronic cases
Enteropathic Arthritis	- Associated with **inflammatory bowel disease (IBD)** (e.g., Crohn's disease, ulcerative colitis) - Sacroiliitis	1. **NSAIDs** (use with caution in IBD) 2. **Sulfasalazine** 3. **Biologics** (e.g., infliximab) if IBD is active
Non-radiographic Axial Spondyloarthritis	- Symptoms similar to ankylosing spondylitis but **no structural changes on X-ray** - Positive MRI findings of inflammation	1. **NSAIDs** 2. **TNF inhibitors** or **IL-17 inhibitors** for severe cases 3. **Physiotherapy**

Shoulder problems

Condition	Notes
Adhesive capsulitis (frozen shoulder)	▪ **Pathophysiology:** a common cause of shoulder pain. cause is not fully understood. ▪ **Risk factors:** diabetes (40% of diabetic patients developing this problem at some stage. occurs more commonly in women after age 50 ▪ **Features:** Dull shoulder pain and restriction of both active and passive movement ▪ **Diagnosis:** Radiographs of the shoulder show osteopenia. Confirmed by arthrography. ▪ **Management:** NSAIDs, physiotherapy, oral and intra-articular corticosteroids. Self-limiting within 18 to 24 months
Supraspinatus tendonitis (Subacromial impingement, painful arc)	▪ Rotator cuff injury ▪ Painful arc of abduction between 60 and 120 degrees ▪ Tenderness over anterior acromion

Elbow pain

Lateral epicondylitis (tennis elbow)	▪ pain and tenderness localised to the lateral epicondyle ▪ pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended ▪ episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks ▪ Treatment: Local steroid/anaesthetic injection
Medial epicondylitis (golfer's elbow)	▪ pain and tenderness localised to the medial epicondyle ▪ pain is aggravated by wrist flexion and pronation ▪ symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement
Radial tunnel syndrome	▪ Most commonly due to compression of the posterior interosseous branch of the radial nerve. ▪ It is thought to be a result of overuse. **Features** ▪ symptoms are similar to lateral epicondylitis making it difficult to diagnose ▪ however, the pain tends to be around 4-5 cm distal to the lateral epicondyle ▪ symptoms may be worsened by extending the elbow and pronating the forearm
Cubital tunnel syndrome	Due to the compression of the ulnar nerve. **Features** ▪ initially intermittent tingling in the 4th and 5th finger ▪ may be worse when the elbow is resting on a firm surface or flexed for extended periods ▪ later numbness in the 4th and 5th finger with associated weakness
Olecranon bursitis	Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients.

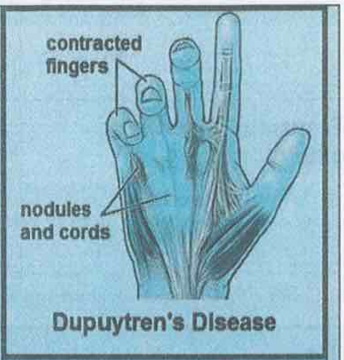
Dupuytren's contracture

Pathophysiology: autosomal-dominant condition → fibroblast proliferation (interleukin-1), and collagen deposition (type III collagen) → painless contracture of the palmar facial bands, → flexion deformities of the fingers (bilateral in 45%; in unilateral cases, the right side is more often affected).

Prevalence: has a **male**: female predominance of 10:1.

Risk factors: alcoholism (10%), diabetes mellitus (8%), smoking, hand trauma, HIV

Management: Surgery followed by physiotherapy. Collagenase therapy may be an alternative to surgery in some cases.



Rheumatoid arthritis seems to protect against the development of Dupuytren disease.

Hip pain in adults

The table below provides a summary of the potential causes of hip pain in adults

Condition	Features
Osteoarthritis	Pain exacerbated by exercise and relieved by rest Reduction in internal rotation is often the first sign Age, obesity and previous joint problems are risk factors
Inflammatory arthritis	Pain in the morning Systemic features Raised inflammatory markers
Referred lumbar spine pain	Femoral nerve compression may cause referred pain in the hip Femoral nerve stretch test may be positive - lie the patient prone. Extend the hip joint with a straight leg then bend the knee. This stretches the femoral nerve and will cause pain if it is trapped
Greater trochanteric pain syndrome (Trochanteric bursitis)	Due to repeated movement of the fibroelastic iliotibial band Pain and tenderness over the lateral side of thigh Most common in women aged 50-70 years
Meralgia paraesthetica	Caused by compression of lateral cutaneous nerve of thigh Typically burning sensation over antero-lateral aspect of thigh
Avascular necrosis	Symptoms may be of gradual or sudden onset May follow high dose steroid therapy or previous hip fracture of dislocation
Pubic symphysis dysfunction	Common in pregnancy Ligament laxity increases in response to hormonal changes of pregnancy

Condition	Features
	Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen
Transient idiopathic osteoporosis	An uncommon condition sometimes seen in the third trimester of pregnancy Groin pain associated with a limited range of movement in the hip Patients may be unable to weight bear ESR may be elevated

Baker's cyst

- The most common mass in the popliteal fossa) is a posterior herniation of the synovium of the knee joint.
- Most commonly caused by osteoarthritis
- Look for a patient with osteoarthritis or rheumatoid arthritis with a swollen calf. A ruptured Baker's cyst is a "pseudophlebitis." Unruptured cysts can be palpated.
- **Investigated by Ultrasonography**

Immunosuppressants

Cyclophosphamide (Alkylating Agent)

Category	Details
Mode of Action	Alkylating agent that **interferes with DNA replication** and **cell division** by cross-linking DNA strands.
Indications	- **Autoimmune diseases**: Systemic lupus erythematosus (SLE), vasculitis, rheumatoid arthritis - **Oncology**: Lymphomas, leukaemias, breast cancer, ovarian cancer
Recommended Doses	- **Autoimmune diseases**: 500-1000 mg/m² IV every 2-4 weeks - **Cancer**: Dose varies (1-5 mg/kg/day) depending on cancer type and protocol
Administration	- **Oral**: Daily or intermittent dosing - **Intravenous (IV)**: Intermittent bolus dosing (e.g., monthly infusion)
Side Effects	- **Hematologic**: Bone marrow suppression, leukopenia - **Gastrointestinal**: Nausea, vomiting - **Urological**: Hemorrhagic cystitis (due to acrolein metabolite) - **Alopecia** (hair loss) - **Infections**: Increased susceptibility to infections
Contraindications	- **Severe bone marrow suppression** - **Severe infections** - Hypersensitivity to cyclophosphamide or other alkylating agents
Pregnancy and Breastfeeding	- **Pregnancy**: Contraindicated; teratogenic and may cause fetal harm (Category D) - **Breastfeeding**: Not recommended; excreted in breast milk and may harm the infant
Special Notes	- **Hemorrhagic cystitis prevention**: Use **MESNA** (uroprotective agent) and ensure adequate hydration - **Monitor**: CBC, renal function, and liver function tests during treatment - Consider **prophylactic antimicrobials** to reduce infection risk

Ciclosporin

Category	Details
Mode of Action	**Calcineurin inhibitor**: Inhibits T-cell activation by blocking the transcription of IL-2 and other cytokines.
Indications	- **Autoimmune diseases**: Rheumatoid arthritis, psoriasis, systemic lupus erythematosus (SLE), nephrotic syndrome - **Organ transplantation**: Prevention of graft rejection (kidney, liver, heart)
Recommended Doses	- **Rheumatoid arthritis / Psoriasis**: 2.5-5 mg/kg/day orally, divided into two doses - **Transplantation**: Initial dose of 5-10 mg/kg/day, adjusted based on blood levels
Administration	- **Oral**: Capsule or oral solution, given in divided doses - **Intravenous (IV)**: For acute use (IV doses are typically one-third of the oral dose)
Side Effects	- **Renal toxicity** (nephrotoxicity) - **Hypertension** - **Hyperlipidaemia** - **Gum hyperplasia** and **hirsutism** - **Infections**: Increased risk of opportunistic infections - **Neurotoxicity**: Tremors, headache, seizures
Contraindications	- **Uncontrolled hypertension** - **Renal impairment** - **Malignancies** - Hypersensitivity to ciclosporin
Pregnancy and Breastfeeding	- **Pregnancy**: Can be used if benefits outweigh risks; monitor fetal growth (Category C) - **Breastfeeding**: Not recommended; excreted in breast milk and may cause immunosuppression in the infant
Special Notes	- **Monitor**: Regular blood monitoring for **serum ciclosporin levels** and renal function - **Drug interactions**: Grapefruit juice and certain medications (e.g., macrolides, antifungals) can affect ciclosporin levels - **Hypertension management**: Monitor and control blood pressure during

Interestingly for an immunosuppressant, ciclosporin is noted to be 'virtually non-myelotoxic'.

Cyclosporine side effects: everything is increased - fluid, BP, K+, hair, gums, glucose)

Tacrolimus

Mode of action: similar to the action of ciclosporin (**inhibits calcineurin**, **reducing IL-2 release**) however it **binds to a protein called FKBP rather than cyclophilin**

Side effects:

- Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less. However, nephrotoxicity and impaired glucose tolerance is more common
- **Many side effects are similar to cyclosporine A, but tacrolimus does not cause gingival hyperplasia or hirsutism**

Mycophenolate mofetil (MMF)

Category	Details
Mode of Action	**Inhibits inosine monophosphate dehydrogenase (IMPDH)**, blocking de novo purine synthesis in T and B lymphocytes, leading to immunosuppression.
Indications	- **Autoimmune diseases**: Systemic lupus erythematosus (SLE), vasculitis, myasthenia gravis - **Organ transplantation**: Prevention of graft rejection (kidney, heart, liver)
Recommended Doses	- **Autoimmune diseases**: 1-3 g/day orally, divided into two doses - **Transplantation**: Initial dose of 1-1.5 g twice daily
Administration	- **Oral**: Capsule, tablet, or oral suspension - **Intravenous (IV)**: For patients unable to take oral formulations
Side Effects	- **Gastrointestinal**: Diarrhoea, nausea, vomiting, abdominal pain - **Hematologic**: Leukopenia, anaemia, thrombocytopenia - **Infections**: Increased risk of opportunistic infections - **Malignancy**: Increased risk of lymphoma and skin cancers
Contraindications	- **Hypersensitivity** to MMF - **Active infections** - **Severe bone marrow suppression**
Pregnancy and Breastfeeding	- **Pregnancy**: Contraindicated (Category D); can cause congenital malformations and pregnancy loss - **Breastfeeding**: Not recommended; excreted in breast milk and may cause immunosuppression in the infant
Special Notes	- **Monitor**: Complete blood count (CBC) and liver function tests regularly - **Infection prophylaxis**: Consider prophylactic antimicrobials during treatment - **Drug interactions**: Avoid concurrent use with antacids or cholestyramine (reduces MMF absorption)

Azathioprine

Category	Details
Mode of Action	**Purine synthesis inhibitor**: Converted to **6-mercaptopurine (6-MP)**, interfering with DNA and RNA synthesis, leading to **suppressed lymphocyte proliferation**.
Indications	- **Autoimmune diseases**: Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) - **Organ transplantation**: Prevention of graft rejection
Recommended Doses	- **Autoimmune diseases**: 1-3 mg/kg/day orally - **Organ transplantation**: 3-5 mg/kg/day initially, adjusted based on response and toxicity
Administration	- **Oral**: Most common route (tablet form) - **Intravenous (IV)**: For patients unable to take oral formulations
Side Effects	- **Hematologic**: Bone marrow suppression (leukopenia, anaemia, thrombocytopenia) - **Gastrointestinal**: Nausea, vomiting, diarrhoea, hepatotoxicity - **Infections**: Increased susceptibility to infections - **Rare**: Pancreatitis, hypersensitivity reactions
Contraindications	- **Hypersensitivity** to azathioprine - **Active infections** - **Severe bone marrow suppression**
Pregnancy and Breastfeeding	- **Pregnancy**: Can be used if benefits outweigh risks (Category D); careful monitoring required - **Breastfeeding**: Not recommended, as azathioprine is excreted in breast milk
Special Notes	- **Monitor**: Regular CBC, liver function tests, and TPMT (thiopurine methyltransferase) levels to avoid toxicity - **Drug interactions**: Concurrent use with **allopurinol** can increase toxicity; dose adjustment needed - **Infection prophylaxis**: Consider in long-term therapy to reduce the risk of infections

Azathioprine (AZA)

Indications
- Inflammatory bowel disease
- Rheumatoid arthritis
- Renal transplantation

Side-effects
- Bone marrow suppression
- Pancreatitis
- Hepatotoxicity
- ↑risk of skin cancers (lymphomas)

Before use

Check (TPMT) Thiopurine Methyltransferase enzyme activity : TPMT enzyme deficiency → azathioprine toxicity → myelosuppression

Mode of Action

Metabolised to the active compound mercaptopurine (6-MP) → inhibits purine synthesis → Impaired DNA synthesis

Interaction

Allopurinol (xanthine oxidase inhibitor) →↓ elimination of 6- MP (the active metabolite of AZA) → ↑ risk of AZA toxicity

Contraindications
- Severe renal or hepatic impairment
- Unknown TPMT status

Dose

initiated at 50 mg and increased by 50 mg every 4 weeks to maximum dose of 2.5 mg/kg daily

Monitoring

CBC every 2 weeks with changes in dose, CBC, LFT, RFT 3 months thereafter.

Use in pregnancy

Generally safe during pregnancy and lactation

Biologic Agents

Category	Details
Mode of Action	Target specific components of the immune system (e.g., **cytokines, immune cells, or receptors**), modulating the immune response. Examples: - **Anti-TNF agents**: Block tumor necrosis factor (e.g., infliximab, adalimumab) - **Anti-CD20 agents**: Deplete B-cells (e.g., rituximab) - **IL-6 inhibitors**: Block interleukin-6 (e.g., tocilizumab)
Indications	- **Autoimmune diseases**: Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, inflammatory bowel disease (IBD) - **Oncology**: B-cell lymphomas (rituximab) - **Transplant rejection prevention**
Recommended Doses	Varies based on the agent and condition: - **Infliximab**: 3-5 mg/kg IV every 8 weeks - **Rituximab**: 375 mg/m² IV weekly (for 4 weeks)
Administration	Administered via **intravenous (IV) infusion** or **subcutaneous injection**.
Side Effects	- **Infusion reactions** (fever, chills, hypotension) - **Infections**: Increased risk of opportunistic infections (e.g., tuberculosis, fungal infections) - **Hematologic**: Neutropenia, anaemia - **Cardiovascular**: Rare risk of heart failure exacerbation

Category	Details
Contraindications	- **Active infections** (e.g., untreated tuberculosis) - Hypersensitivity to the agent - **Heart failure** (for anti-TNF agents)
Pregnancy and Breastfeeding	- **Pregnancy**: Generally considered safe for use if benefits outweigh risks, especially in the second and third trimesters - **Breastfeeding**: Some agents (e.g., infliximab) may be compatible with breastfeeding; consult specific guidelines
Special Notes	- **Screening for latent infections** (e.g., tuberculosis) before starting therapy - Monitor for **signs of infection** during therapy - **Combination therapy** with DMARDs (e.g., methotrexate) is common to improve outcomes and reduce immunogenicity

mTOR Inhibitors (e.g., Sirolimus, Everolimus) Summary

Category	Details
Mode of Action	**Inhibit the mammalian target of rapamycin (mTOR)** pathway, blocking T-cell proliferation and reducing immune response by interfering with IL-2 signaling.
Indications	- **Organ transplantation**: Prevention of graft rejection (kidney, liver) - **Oncology**: Treatment of renal cell carcinoma, breast cancer, and neuroendocrine tumors
Recommended Doses	- **Sirolimus**: 2-5 mg/day orally - **Everolimus**: 0.75-1 mg twice daily (in transplant patients); higher doses for cancer treatment
Administration	**Oral** (tablet or solution) taken once or twice daily depending on the condition.
Side Effects	- **Delayed wound healing** - **Hyperlipidemia** (increased cholesterol and triglycerides) - **Infections**: Increased risk of opportunistic infections - **Mouth ulcers** and stomatitis - **Pulmonary toxicity**: Non-infectious pneumonitis in rare cases
Contraindications	- **Severe infections** - Hypersensitivity to sirolimus or everolimus - Avoid use in **patients with poor wound healing capacity**
Pregnancy and Breastfeeding	- **Pregnancy**: Use only if benefits outweigh risks (Category C); teratogenic in animal studies - **Breastfeeding**: Not recommended due to potential harm to the infant
Special Notes	- **Monitoring**: Regular blood tests to check **serum drug levels**, lipid profile, and renal function - **Drug interactions**: Grapefruit juice and certain antifungal agents can increase drug levels - Use with **caution** in patients at risk for hyperlipidemia or with impaired wound healing

Glucocorticoid Agents

Category	Details
Mode of Action	Bind to **glucocorticoid receptors**, altering gene expression to suppress inflammation and immune responses by inhibiting cytokines and leukocyte migration.
Indications	- **Autoimmune diseases**: Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), vasculitis - **Allergic conditions**: Asthma, anaphylaxis - **Organ transplantation**: Prevention of rejection - **Endocrine disorders**: Adrenal insufficiency (e.g., Addison's disease)
Recommended Doses	- Varies by agent and indication - **Prednisolone**: 5-60 mg/day (depending on severity) - **Dexamethasone**: 0.5-10 mg/day - **Hydrocortisone**: 20-100 mg/day
Administration	- **Oral**: Tablets or liquid (most common) - **Intravenous (IV)**: For severe cases (e.g., methylprednisolone) - **Topical or inhaled**: For localized inflammation
Side Effects	- **Metabolic**: Hyperglycaemia, weight gain, fluid retention, osteoporosis - **Endocrine**: Adrenal suppression, Cushing's syndrome - **Infections**: Increased risk of infections - **Psychiatric**: Mood changes, insomnia, psychosis - **Ophthalmic**: Cataracts, glaucoma
Contraindications	- **Uncontrolled infections** - **Peptic ulcer disease** - Severe **osteoporosis** - **Uncontrolled diabetes** or **hypertension**
Pregnancy and Breastfeeding	- **Pregnancy**: Can be used if necessary (Category C); monitor for fetal growth restriction - **Breastfeeding**: Generally safe, but monitor infant for adrenal suppression with prolonged high doses
Special Notes	- **Monitor**: Blood glucose, bone density, blood pressure, and signs of infection during long-term use - **Tapering**: Gradual dose reduction is necessary to prevent adrenal insufficiency - **Prophylaxis**: Consider bone protection (e.g., calcium, vitamin D, bisphosphonates) during long-term therapy

Non-steroidal anti-inflammatory drugs (NSAID)

Comparison of NSAIDs

Consideration	Comments
COX Selectivity	- **Non-selective**: Ibuprofen, Naproxen - **Partially COX-2 selective**: Diclofenac - **COX-2 selective**: Celecoxib
Analgesic Potency	No significant differences in treating **RA, gout, and osteoarthritis** across most NSAIDs.
Liver Toxicity	Rare, but can occur with most NSAIDs. **Piroxicam** has the least hepatic effects.
Gastrointestinal Side Effects	- Linked to **COX-1 inhibition**; **COX-2 inhibitors** show fewer GI side effects. - **Diclofenac** (partially COX-2 selective) has lower GI toxicity than other non-selective NSAIDs.
Cardiovascular Risk	- **COX-2 inhibitors** increase cardiovascular risks. - **Diclofenac** has risks similar to COX-2 inhibitors and should be avoided in patients with IHD, PAD, CVA, or HF. - **Etoricoxib** should be avoided in hypertension. - **Naproxen** (1000 mg/day or less) and **low-dose ibuprofen** (≤1200 mg/day) have the safest cardiovascular profiles.
Acute Kidney Injury	No significant difference in the risk of acute kidney injury between NSAIDs.
Haematologic Effects	- Inhibit **platelet aggregation** and prolong bleeding time. - **Piroxicam** has the strongest effect on platelet function due to its long half-life (50 hours).
Ankylosing Spondylitis	**Indomethacin** is most effective, followed by **naproxen**.
Headache Treatment	- **Naproxen** and **aspirin** are preferred for muscle contraction headaches. - **Indomethacin** should be avoided due to vasoconstrictive properties but is effective for **chronic paroxysmal hemicrania** and **hemicrania continua**. - **Naproxen** is highly evaluated for migraines, reducing both frequency and severity.
Association with Porphyria	- **Ketoprofen** and **diclofenac** are associated with acute porphyria. - **Indomethacin, mefenamic acid, ibuprofen,** and **naproxen** are safe for use in patients at risk of porphyria. - **Naproxen** may cause pseudoporphyria (photosensitivity and blistering without biochemical evidence of porphyria).
Drug Interactions	- **Reduces efficacy of antihypertensives**. - Co-administration with **lithium** may cause **lithium toxicity**. - Co-administration with **methotrexate** may result in **methotrexate toxicity**.

Celecoxib is an NSAID that is safe to use in patients with gastritis or gastric ulcers as it does not affect COX1 action at the stomach (since COX-1 is involved in gastric cytoprotection).

Advantages

- **Reduced incidence of upper gastrointestinal side effects.**
- **Lower level of anti-platelet activity than naproxen (platelet aggregation is not affected by COX-2.)**

Dose: 200 mg once daily (maximum 200 mg twice daily)

Renal dose: CrCl >30 No dosage adjustment. Avoid use if CrCl ≤30 mL/minute.

Hepatic dose: Reduce dose by 50% in Moderate hepatic impairment. Contraindicated in severe impairment.

Avoid in patients with significant cardiovascular disease.

Co-prescribe gastroprotective treatment (a proton pump inhibitor) with NSAIDs

If an NSAID is needed, use ibuprofen (1200 mg a day or less) or naproxen (1000 mg a day or less).

Chronic paroxysmal hemicrania, characterised by daily headaches with an attack frequency of greater than 15 episodes per 24 hours, is aborted by indomethacin.

Celecoxib and Diclofenac have lower GI toxicity, whereas naproxen has the least cardiotoxic effects. Naproxen is the NSAID of choice in patients with high cardiovascular risk.

2nd Edition

Internal Medicine Passport

For Practice & Exams

এই পেজ টা পরে ঠিক করতে হবে

By

Dr. Yousif Abdallah Hamad

Chapter- 9

Infectious diseases

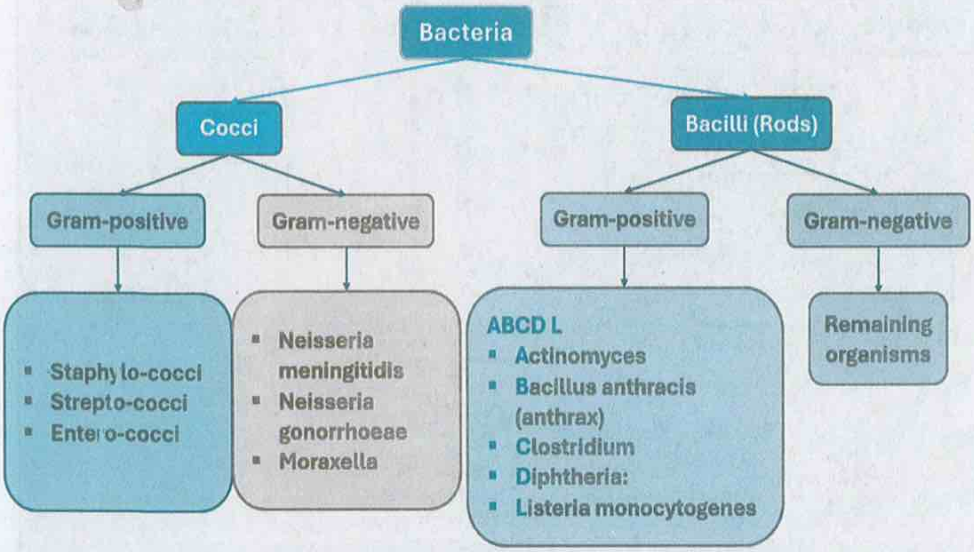
Updated

2025

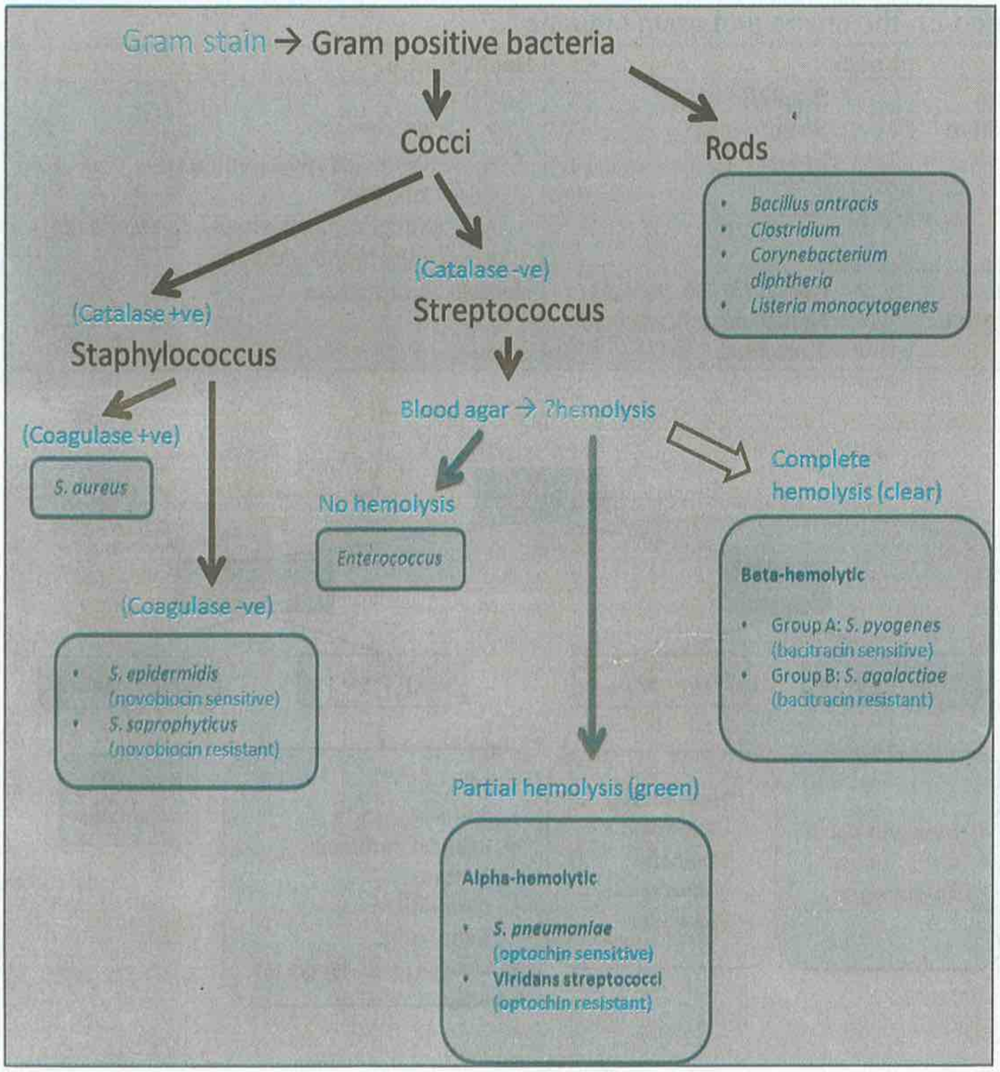
Classification of bacteria

Based on the shape and gram staining

	Cocci	Bacilli (Rods)
Gram positive	▪ **Staphylo**-cocci ▪ **Strepto**-cocci ▪ **Entero**-cocci	ABCD L ▪ *Actinomyces* ▪ *Bacillus anthracis* (anthrax) ▪ *Clostridium* ▪ Diphtheria: *Corynebacterium diphtheria* ▪ *Listeria monocytogenes*
Gram negative	▪ ***Neisseria** meningitidis* ▪ ***Neisseria** gonorrhoeae* ▪ ***Moraxella***	Remaining organisms

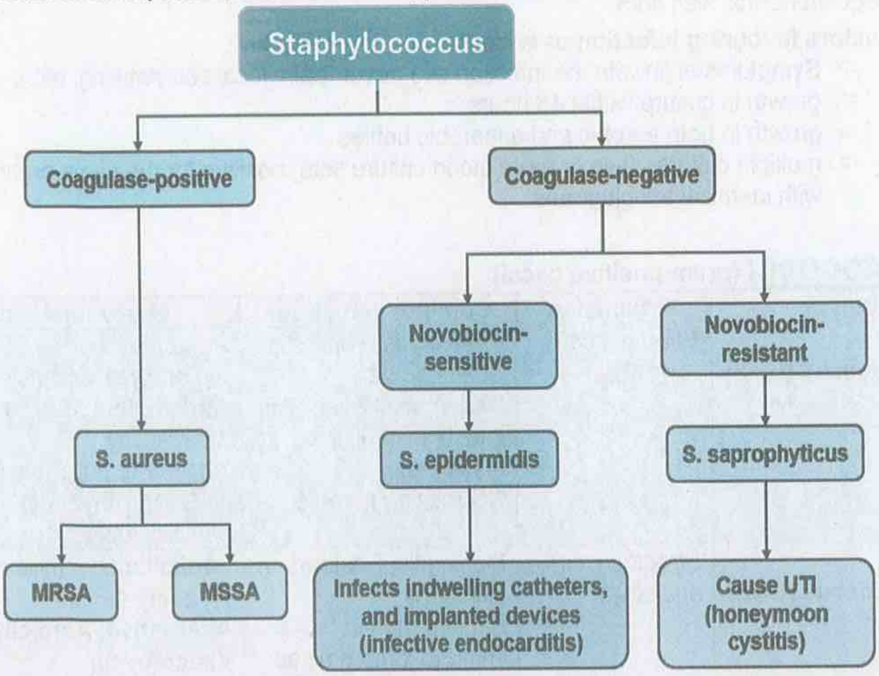


Gram-positive bacteria



Staphylococci

Gram-positive cocci, facultative anaerobes, produce catalase



Sub-types

Sub-Type	Organisms	Common Infections	Preferred Antibiotics
Coagulase-positive Staphylococci	*Staphylococcus aureus*	Skin and soft tissue infections (cellulitis, abscesses), osteomyelitis, pneumonia, infective endocarditis, **toxic shock syndrome**, food poisoning	**Methicillin-sensitive (MSSA):** Flucloxacillin, Cefazolin **Methicillin-resistant (MRSA):** Vancomycin, Daptomycin, Linezolid
Coagulase-negative Staphylococci (CoNS)	*Staphylococcus epidermidis*	Prosthetic device infections (catheters, **central line**, prosthetic joints), bacteremia, **endocarditis** (especially in prosthetic valves)	Vancomycin (especially for resistant strains), Rifampin
	Staphylococcus saprophyticus	**the 2nd most common cause of UTI after E.coli**	Nitrofurantoin, Trimethoprim-sulfamethoxazole (TMP-SMX), Fosfomycin

Distinguishing between contamination and true infection:

- A positive blood culture for CoNS → Infection (25%) or contaminants (75%): The most frequent normal skin flora.
- **Factors favouring infection over contamination include:**
  - ⇨ Symptoms align with the infection site (fever, pain, localised swelling, etc.).
  - ⇨ growth in culture within 48 hours
  - ⇨ growth in both aerobic and anaerobic bottles
  - ⇨ multiple cultures (two or more blood culture sets) positive for the same organism with identical antibiograms

Streptococci (gram-positive cocci)

Subtype	Organisms	Common Infections	Best Antibiotics
Group A Streptococcus (GAS)	*Streptococcus pyogenes*	Pharyngitis, Tonsillitis, Scarlet Fever, Rheumatic Fever, Skin infections (cellulitis, erysipelas), Necrotizing fasciitis	**Penicillin V or G:** 250-500 mg orally, 2-4 times/day **Amoxicillin:** 500 mg orally, 3 times/day **Alternative: Clindamycin** or **Erythromycin** in penicillin allergy
Group B Streptococcus (GBS)	*Streptococcus agalactiae*	Meningitis, Postpartum infections, Bacteraemia in immunocompromised adults	**Penicillin G:** 5 million units IV, every 4-6 hrs **Alternative: Ampicillin** or **Vancomycin**
Group C and G Streptococci	*S. dysgalactiae*, *S. equisimilis*	Pharyngitis, Skin infections, Endocarditis	**Penicillin G or Amoxicillin**, same as GAS
Streptococcus pneumoniae (Pneumococcus)	*Streptococcus pneumoniae*	Pneumonia, Otitis media, Meningitis, Sinusitis, Bacteraemia	**Amoxicillin:** 500 mg 3 times/day **Ceftriaxone:** 1-2 g IV daily **In resistant cases: Vancomycin** or **Levofloxacin**
Viridans Group Streptococci	*S. mitis*, *S. sanguinis*, *S. mutans*	Endocarditis (subacute), Dental caries	**Penicillin G:** 12-24 million units/day IV, divided doses **Gentamicin:** 1 mg/kg every 8 hrs (in combination therapy for endocarditis)
Enterococcus	*E. faecalis*, *E. faecium*	Urinary Tract Infections (UTIs), Endocarditis, Intra-abdominal infections	**Ampicillin:** 2 g IV every 4-6 hrs **In resistant strains: Vancomycin** or **Linezolid**

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Aspect	Details
Definition	MRSA is a strain of *Staphylococcus aureus* resistant to methicillin and other beta-lactam antibiotics, including penicillin, oxacillin, and cephalosporins.
Mechanism	MRSA develops resistance by **mutation in penicillin-binding proteins**. It acquires the **mecA gene**, which encodes an altered penicillin-binding protein (PBP2a) with a low affinity for beta-lactam antibiotics. This protein prevents antibiotic binding and action.
Types of MRSA	- **Healthcare-associated MRSA (HA-MRSA):** Acquired in healthcare settings. - **Community-associated MRSA (CA-MRSA):** Acquired outside healthcare facilities, often causing skin infections.
Common Infections	- Skin and soft tissue infections (cellulitis, abscesses). - Pneumonia (especially in ventilated patients). - Bloodstream infections (bacteraemia). - Endocarditis and osteomyelitis.
Risk Factors	- Hospitalization or recent surgery. - Indwelling devices (e.g., catheters). - Immunocompromised status. - Crowded environments (e.g., prisons, gyms).
Diagnostic Tests	- **Culture:** from infected site (wound, sputum, blood). - **Antibiotic susceptibility testing:** to confirm resistance. - **PCR for mecA gene:** rapid confirmation of MRSA.
Treatment	**First-line drugs:** - **Vancomycin:** 15-20 mg/kg IV every 8-12 hrs (requires therapeutic monitoring). - **Linezolid:** 600 mg orally or IV twice daily. - **Daptomycin:** 4-6 mg/kg IV daily (used for bloodstream infections).
Alternative Treatments	- **Clindamycin:** 600 mg every 8 hours for mild to moderate infections. - **Trimethoprim-sulfamethoxazole (TMP-SMX):** 160/800 mg twice daily (CA-MRSA). - **Tetracyclines:** e.g., doxycycline, 100 mg twice daily.
Prevention	- Hand hygiene in healthcare settings (**the most effective method**) - Screening of high-risk patients (e.g., pre-surgery). - Decolonization with **mupirocin nasal ointment** and **chlorhexidine wash** in carriers.

Cellulitis

Definition: Inflammation of the skin and subcutaneous tissues.

Causes

- **Beta-hemolytic streptococci, usually group A Streptococcus (i.e., S. pyogenes), are the most common cause of cellulitis.** It has a predilection for diabetic patients and is the likeliest causative organism in diabetics
- **Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA), is the most common cause of skin abscess but is a less common cause of cellulitis.**

Features

- commonly occurs on the shins
- erythema, pain, swelling
- systemic upset such as fever
- cellulitis **does not** have sharp, well-defined borders, unlike an erysipelas infection.

Eron classification of cellulitis:

Class	Features
I	No signs of systemic toxicity and no uncontrolled co-morbidities
II	**Systemically unwell patient or systemically well but with a co-morbidity** (for example, peripheral arterial disease, chronic venous insufficiency, or morbid obesity).
III	**Significant systemic upset** (e.g., acute confusion, tachycardia, tachypnoea, hypotension) or unstable co-morbidities or a limb-threatening infection due to vascular compromise
IV	**Sepsis or a severe life-threatening infection** such as necrotizing fasciitis
Interpretation	• **Eron Class III or Class IV cellulitis → Admission** for intravenous antibiotics • **Eron Class II cellulitis**: *Admission may not be necessary.*

Management

- **Mild to moderate cellulitis**
  - ➪ 1st line → **flucloxacillin:** (bactericidal anti-staphylococcus and anti-streptococcus) 500 mg to 1 g/6 hourly for 5 to 7 days, orally **or** 1 g to 2 g/6 hourly IV (NICE & BNF recommendation). MRSA is resistant to flucloxacillin.
  - ➪ **If the patients is allergic to penicillin → Clarithromycin** (500 mg twice a day orally) or **Erythromycin** (in pregnancy): 500 mg four times daily, or **Doxycycline** (200 mg on the first day then 100 mg once daily).
- **If infection is near the eyes or nose:**
  - ➪ **First-choice:** Co-amoxiclav (500/125 mg three times a day orally or 1.2 g three times a day intravenously).
  - ➪ **If the patient is allergic to penicillin → Clarithromycin** 500 mg twice daily **PLUS Metronidazole** 500 mg three times a day
- **Severe cellulitis** (eg, evidence of tissue hypoperfusion or organ dysfunction or neutropenia)
  - ➪ **Flucloxacillin + Co-amoxiclav** or **Ceftriaxone** (2 g once a day)
  - ➪ Vancomycin (15 to 20 mg/kg every 8 to 12 hours) **PLUS** Cefepime (2 g IV every eight hours)

- **If MRSA is suspected or confirmed:** (systemic toxicity (eg, fever, tachycardia), purulent wound drainage, known MRSA colonization or infection, injection drug use, immunocompromise)
  - ⇨ **Vancomycin:** 15 mg/kg to 20 mg/kg two or three times a day intravenously (maximum 2 g per dose), adjusted according to serum vancomycin concentration
  - ⇨ **Teicoplanin:** Initially 6 mg/kg every 12 hours for three doses, then 6 mg/kg once a day intravenously
  - ⇨ **Linezolid** (if vancomycin or teicoplanin cannot be used; specialist use only): 600 mg twice a day orally **or** 600 mg twice a day intravenously.
- **Infection due to an organism with an extended-spectrum beta-lactamase (ESBL):** Meropenem (1 g IV every eight hours) PLUS vancomycin (15 to 20 mg/kg every 8 to 12 hours).

Necrotising fasciitis

Definition: infection of the deep soft tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat.

Classification (according to the causative organism):

- **Type 1** caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics)
- **Type 2** commonly caused by group A *Streptococci, Streptococcus pyogenes*

Features

- acute onset
- painful, erythematous lesions (out of proportion to skin findings)
- extremely tender over infected tissue

Management

- **Urgent surgical referral for exploration & debridement**
- A carbapenem or piperacillin-tazobactam (Tazocin) **plus** an agent with activity against MRSA **plus** Clindamycin (for its antitoxin effects against toxin-elaborating strains of beta-hemolytic streptococci and S. aureus)

Toxic shock syndrome (TSS)

Definition: a toxin-mediated, life-threatening illness that results in hypotension and multiorgan failure

Causes

- *Staphylococcus aureus*, which releases enterotoxin type B (i.e. toxic shock syndrome toxin-1), **commonly associated with an infected cutaneous site.**
- *Streptococcus pyogenes*, which releases pyogenic exotoxins, associated with extended tampon use, postpartum infections

Risk factors

- **Recent menstruation**
- Recent use of barrier contraceptives such as diaphragms and **vaginal sponges**
- **Vaginal tampon** use (especially prolonged)
- Recent childbirth
- Recent surgery,
- Current S. aureus infection.

Features
- Rapid onset of non-specific symptoms (e.g., fever, chills, myalgias, headache)
- Diffuse macular erythroderma followed by desquamation one to two weeks later (**staphylococcal scalded skin syndrome)**
- Multi-organ system failure.

Treatment
- Supportive care in an ICU,
- Early empirical antibiotic treatment and further culture-sensitive antibiotic treatment.
  - ⇨ Vancomycin plus clindamycin plus Tazocin
  - ⇨ clindamycin (a bacteriostatic antibiotic acts by inhibiting protein synthesis within bacteria)→↓ exotoxin expression →removing the mediators of TSS.
- Surgical debridement may be needed

> ***Staphylococcus aureus*** **→ Toxic shock syndrome toxin → binds to major histocompatibility complex II and T cell receptor → overwhelming release of cytokines → shock.**

Osteomyelitis

Definition: Osteomyelitis: infection of bone marrow and bone

Causes
- ***Staph. aureus*** **is the most common cause,** followed by *Pseudomonas*
- ***Salmonella*** **species is the commonest cause in patients with sickle-cell anaemia.**
- Pasteurella multocida seen in cases caused by cat and dog bites

Location: The lumbar spine is most commonly affected in **Haematogenous osteomyelitis**, followed by the thoracic and cervical regions and metaphysis of long bones.

Risk factors
- Diabetes mellitus
- Sickle cell anaemia
- Intravenous drug user
- Immunosuppression due to either medication or HIV
- Alcohol excess

Investigations
- **MRI is the imaging modality of choice**.
- X-ray shows the best initial screening test.
  - ⇨ **Early stages (< 2 weeks of symptoms onset): typically no pathological findings**
  - ⇨ Later stages: bone destruction, sequestrum formation, periosteal reactions
  - ⇨ Lytic lesion with sclerotic margins (**Brodie's abscess**), a form of chronic osteomyelitis
- Bone biopsy: **confirmatory test**

Management

- **Initial empiric therapy:** Vancomycin **plus** a third- or fourth-generation cephalosporin (such as ceftriaxone, ceftazidime, or cefepime)
- **Culture-based IV antibiotics:**
  - ⇨ **Staphylococci (methicillin-susceptible):** Flucloxacillin (2 g IV every 6 hours), Cefazolin (2 g IV every 8 hours) or Ceftriaxone (2 g IV every 24 hours)
  - ⇨ **Staphylococci (methicillin-resistant):** Vancomycin (Loading dose: 20 mg/kg followed by maintenance dose 15 to 20 mg/kg every 8 to 12 hours)
  - ⇨ **Gram-negative organisms:** Meropenem (1 g IV every 8 hours), Cefepime (2 g IV every 8 to 12 hours), Ceftazidime (2 g IV every 8 hours), Levofloxacin (750 mg orally or IV once daily)
  - ⇨ **Enterococci:**
    - Monotherapy: Vancomycin
    - Combination therapy: Ampicillin (12 g IV every 24 hours, divided in 6 doses) **plus** Ceftriaxone (2 g IV every 12 to 24 hours)
  - ⇨ **Streptococci (penicillin-sensitive):** Ceftriaxone, Ampicillin or Vancomycin
- **Oral antibiotic to complete 6 weeks**
  - ⇨ **Staphylococci (methicillin-susceptible):** Flucloxacillin (500 mg 4 times daily)
  - ⇨ **Staphylococci (methicillin-resistant):** Doxycycline (100 mg twice daily), Clindamycin (600 mg 3 times daily)
  - ⇨ **Gram-negative organisms:** Levofloxacin or Ciprofloxacin (500 mg twice daily)
  - ⇨ **Penicillin-sensitive streptococci and enterococci:** Amoxicillin (500 mg 2 to 3 times daily)

Vertebral Osteomyelitis & Discitis

Aspect	Details
Pathogenesis	Hematogenous spread from distant infection (most common) or adjacent soft tissue infection. *Staphylococcus aureus* is the leading pathogen.
Risk Factors	Intravenous drug use, immunosuppression, diabetes, recent surgery
Clinical Features	- Musculoskeletal pain, often with fever and recent bacteremia - Non-mechanical back or neck pain (worsening at rest or night) - Local tenderness on percussion of posterior spinous processes
Investigations	- **Inflammatory markers**: Elevated WBC, CRP, ESR - **Blood cultures**: Positive in 50-70% of cases - **MRI: The most sensitive imaging method** - **Biopsy**: Confirms diagnosis (if required) - **Concurrent infections**: Evaluate for endocarditis if indicated
Differential Diagnosis	- **Epidural abscess:** Presents with neurological signs (lower limb involvement) - **Osteoporotic fracture**: X-ray shows vertebral collapse - **Spinal metastases**: Less likely without X-ray changes
Treatment	- **Empiric Antibiotics**: Start after obtaining cultures - **Minimum Duration**: Six weeks - **Empiric Regimen**: Vancomycin + Ceftriaxone (2 g IV daily) or **Ciprofloxacin** (400 mg IV every 12 hrs or 500–750 mg orally twice daily)

Osteomyelitis: MRI is the imaging modality of choice

Osteomyelitis pathogens:

- **The causative bacteria is *Staphylococcus aureus* until proven otherwise.**
- **Patients with sickle cell disease have a predisposition to develop osteomyelitis due to *Salmonella* species.**

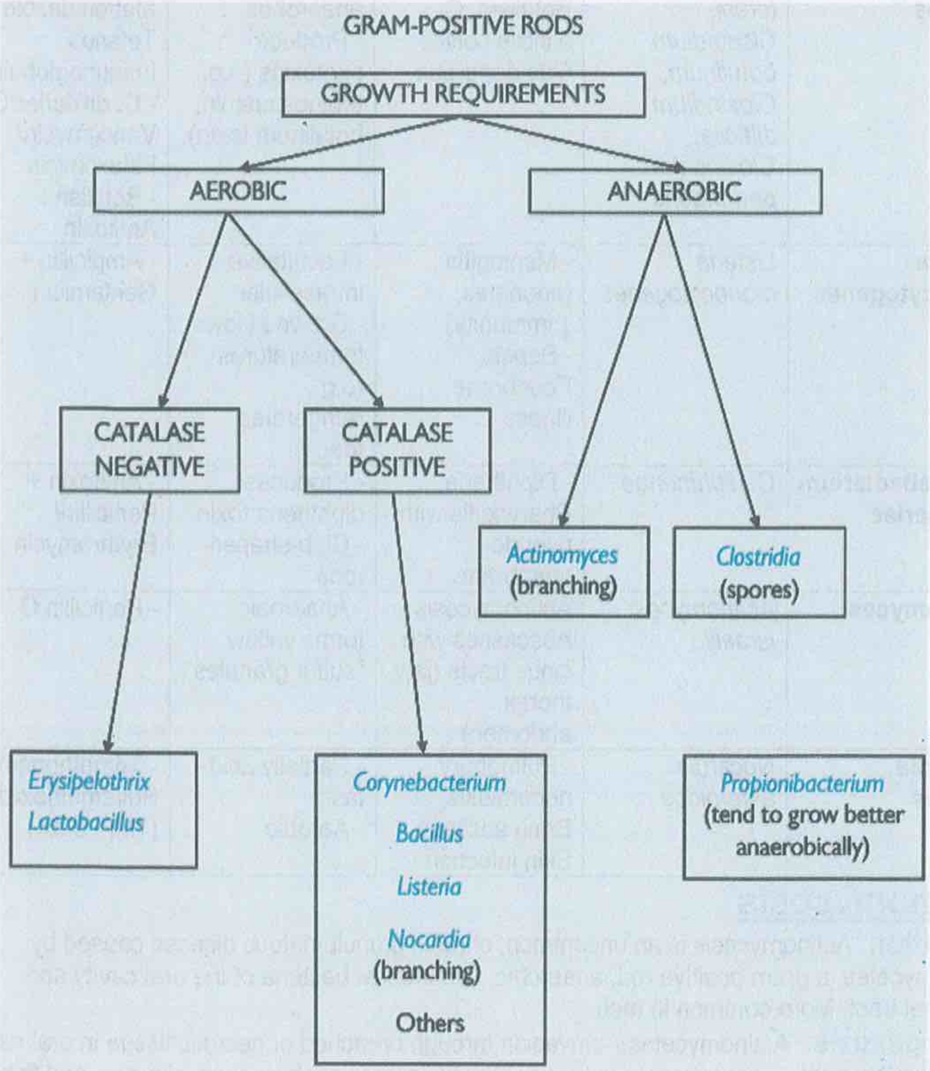
Enterococcus (Gram-positive cocci of intestinal origin)

Aspect	Details
Organisms	- ***Enterococcus faecalis:*** More common, associated with community and healthcare infections - ***Enterococcus faecium:*** Less common but more resistant (often vancomycin-resistant, VRE).
Common Infections	- **Urinary tract infections (UTI)**: Often catheter-associated. - **Endocarditis**: Associated with prosthetic heart valves or structural heart disease. - **Intra-abdominal infections**: Post-surgical or spontaneous. - **Biliary tract infections** - **Bacteremia/Sepsis**: Particularly in immunocompromised or hospitalised patients. - **Wound infections**: Common after trauma or surgical procedures.
Antibiotics	- **Ampicillin**: First-line for non-resistant strains; 1–2 g IV every 4–6 hrs. - **Vancomycin**: Used for ampicillin-resistant strains; 15–20 mg/kg IV every 8–12 hrs. - **Linezolid**: Effective against vancomycin-resistant enterococcus (VRE); 600 mg IV/orally every 12 hrs. - **Daptomycin**: Alternative for VRE infections; 4–6 mg/kg IV daily. - **Nitrofurantoin or Fosfomycin**: For uncomplicated UTIs; Nitrofurantoin 100 mg orally twice daily for 5–7 days, Fosfomycin 3 g orally once.
Key Considerations	- **VRE strains** are more common in *E. faecium* infections. - Combination therapy (e.g., ampicillin + gentamicin) is used in endocarditis. - Enterococcus shows intrinsic resistance to many antibiotics (e.g., cephalosporins). - Close monitoring is required in cases of bacteremia, as persistent infection may indicate endocarditis.

Gram-positive rod

Gram-positive rod = ABCD L

- *Actinomyces*
- *Bacillus anthracis* (anthrax)
- *Clostridium*
- Diphtheria: *Corynebacterium diphtheria*
- *Listeria monocytogenes*



Gram-Positive Rods (Bacilli)

Type	Examples	Common Infections	Distinct Features	Treatment
Bacillus species	*Bacillus anthracis* (Anthrax), *Bacillus cereus*	- Anthrax: Cutaneous, inhalational, gastrointestinal - Food poisoning (B. cereus)	- *B. anthracis*: Encapsulated, spore-forming - *B. cereus*: Foodborne illness from reheated rice	- Ciprofloxacin or Doxycycline (for anthrax) - Symptomatic for food poisoning
Clostridium species	*Clostridium tetani*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*	- Tetanus, Botulism, C. difficile colitis, Gas gangrene	- Spore-forming anaerobes - Produce exotoxins (e.g., tetanospasmin, botulinum toxin)	- **Tetanus:** Metronidazole + Tetanus Immunoglobulin - **C. difficile:** Oral Vancomycin/ Fidaxomicin - Botulism: Antitoxin
Listeria monocytogenes	*Listeria monocytogenes*	- Meningitis (neonates, ↓ immunity) - Sepsis, Foodborne illness	- Facultative intracellular - Grows at low temperatures (e.g., refrigerated foods)	- Ampicillin + Gentamicin
Corynebacterium diphtheriae	*C. diphtheriae*	- Diphtheria: Pharyngitis with pseudo-membrane	- Produces diphtheria toxin - Club-shaped rods	- Antitoxin + Penicillin/ Erythromycin
Actinomyces	*Actinomyces israelii*	Actinomycosis: Abscesses with sinus tracts (jaw, thorax, abdomen)	- Anaerobic, forms yellow "sulfur granules"	- Penicillin G
Nocardia species	*Nocardia asteroides*	- Pulmonary nocardiosis, Brain abscess, Skin infection	- Partially acid-fast - Aerobic	- Trimethoprim-Sulfamethoxazole (TMP-SMX)

Actinomycosis

Definition: Actinomycosis is an uncommon, chronic granulomatous disease caused by actinomycetes, a gram-positive rod, anaerobic, commensal bacteria of the oral cavity and intestinal tract. More common in men.

Pathogenesis: Actinomycetes → invasion through breached or necrotic tissue in oral cavity and intestinal tract → granulomatous tissue, fibrosis, necrosis, abscesses, sinuses, and fistulas

Predisposing conditions: breaching of oral mucosa (tooth extractions, jaw fractures, foreign bodies)

Features

- **Cervicofacial actinomycosis:** the most common Actinomyces infection → odontogenic, abscess or cellulitis of the floor of the mouth.
- **Abdominal Actinomycosis:** Chronic nonspecific symptoms (fatigue, fever, weight loss, and abdominal pain).
- Palpable mass, visible sinus tracts, or fistulas.

Diagnosis

- **Require a high index of suspicion** in patients presenting with chronic nonspecific abdominal symptoms and abdominal mass.
- **CT abdomen** is the most useful imaging for abdominal actinomycosis → solid masses with focal low-attenuation areas or cystic masses with thickened walls.
- **Histopathology:** a definitive diagnosis → identification of actinomycotic sulfur granules (represent colonies of Actinomyces) and/or culture of Actinomyces.

Differential diagnosis

- Nocardiosis may present similarly and has a similar appearance on microscopy.
- Difference between Actinomyces spp. and Nocardia spp:
  - ⇨ In culture: Actinomycetes grow in anaerobic conditions and Nocardia do not.

Treatment

- **Medical treatment:**
  - ⇨ Penicillin is the preferred choice (penicillin G 10 to 20 million units daily in divided doses) for 2- 4 weeks. Followed by oral for 2 to 6 months for mild disease and 6 to 12 months for severe disease.
  - ⇨ For patients who cannot take penicillin → ceftriaxone is an alternative.
  - ⇨ For penicillin- and cephalosporin-allergic patients → doxycycline
- **Surgical management:** not necessary for mild infections. Many patients undergo resection before the diagnosis. Initial medical treatment is reasonable if diagnosed prior to surgery. Indicated in complicated cases.

Bacillus anthracis (anthrax)

Caused by: *Bacillus anthracis*, a **gram-positive rod**, aerobic, non-motile, spore and exotoxin-forming bacteria with a capsule protects against phagocytosis (the only bacterial with polypeptide capsule)

Spread by: direct skin contact, inhalation or ingestion of spores from carcasses (dead animal bodies)

Forms:

- **Cutaneous anthrax:** (the **commonest form**): direct skin contact of spores → small, painless, pruritic papule that quickly enlarges and develops a central vesicle or bulla, followed by erosion, resulting in a necrotic ulcer with a **black, depressed eschar.**

- **Inhalation anthrax:** inhalation of spores → flu-like symptoms (myalgia, fever, and malaise) for 4-5 days, followed by progressive respiratory symptoms (severe dyspnea, hypoxemia, and shock).
- **GIT anthrax:** ingestion of spores → necrotic peptic ulcers which can result in hemorrhage. Associated with oropharyngeal lesions in the mouth and throat, with painful edema in the neck, pharyngitis, and cervical lymphadenopathy.
- **Anthrax meningitis:** occurs in a third of patients with systemic anthrax. Associated with parenchymal brain hemorrhage → grossly bloody cerebrospinal fluid (CSF) and rapid progression to delirium or coma.

Risk factors

- Exposure to animals & animals hide (skin)
- Bioterrorism

Pathophysiology

- Anthrax release **edema toxin** → performs the same function as **adenylate cyclase** → ↑ **cAMP** → black eschar with edematous borders, vasodilation and hypotension.

Diagnosis: Positive culture, serology, or PCR

Management

- **Systemic anthrax:**
  - ⇨ **IV antibiotics**
    - **Systemic anthrax with suspected meningitis:** IV ciprofloxacin plus meropenem plus linezolid for at least 3 weeks.
    - **Systemic anthrax (eg, inhalation anthrax) without meningitis:** IV ciprofloxacin plus either clindamycin or linezolid for at least 2 weeks.
  - ⇨ **Antitoxin therapy** (monoclonal antibodies raxibacumab and obiltoxaximab + anthrax immunoglobulin)
  - ⇨ **Glucocorticoids**
- **Cutaneous anthrax without systemic involvement:**
  - ⇨ single oral antibiotic (ciprofloxacin, doxycycline, levofloxacin, or moxifloxacin)
  - ⇨ If there are head or neck involvement or extensive edema → treat like systemic anthrax

Cutaneous anthrax

Clostridium

Gram-positive rod, spore-forming, anaerobic bacteria.

Species: C. perfringens, C. difficile, C. tetani, & C. botulinum

Clostridium perfringens → Clostridial myonecrosis (gas gangrene) a life-threatening muscle infection

- **Risk factors:** Traumatic wounds with vascular compromise (eg, crush injuries) → create an anaerobic environment that is ideal for proliferation of clostridia.
- **Features**: severe muscle pain and tenderness . tense skin with pale, bronze or purple discoloration and may have overlying bullae. Signs of systemic toxicity (fever and tachycardia, followed by shock and multiorgan failure). crepitus in the soft tissue is the most sensitive sign
- **Diagnosis:**
  - ⇨ Blood and tissue cultures → large gram-variable rods (definitive diagnosis)
  - ⇨ CT or MRI can reveal gas in deep tissues.
  - ⇨ Histopathology → tissue destruction with a characteristic absence of inflammatory cells.
- **Treatment:**
  - ⇨ Aggressive surgical debridement
  - ⇨ Antibiotics: Initial empiric antibiotic: Piperacillin-tazobactam (4.5 g IV every eight hours) PLUS clindamycin (900 mg IV every eight hours) is the preferred option. Definitive antibiotic after culture result: penicillin (3 to 4 million units IV every four hours) plus clindamycin (900 mg IV every eight hours)

Clostridium difficile (C. diff) → pseudomembranous colitis and diarrhea

- **Risk factors:** recent antibiotics use (fluoroquinolones, clindamycin, cephalosporins, and penicillins), proton-pump inhibitors, age >65 and recent hospitalization.
- **Features:** watery diarrhea (≥3 loose stools in 24 hours), lower abdominal pain and cramping, low-grade fever, and leukocytosis..
- **Complications:** Toxic megacolon & colonic perforation
- **Investigations:**
  - ⇨ Positive nucleic acid amplification test (NAAT) for C. difficile toxin gene or a positive stool test for C. difficile toxin.
  - ⇨ Abdominal X-ray (if toxic megacolon is suspected) → dilated colon
  - ⇨ Abdominal CT → marked thickening of the colonic wall & pericolonic stranding
  - ⇨ Sigmoidoscopy/colonoscopy: not always necessary (if laboratory evaluation is unclear) → pseudomembranes
- **Management**
  - ⇨ Discontinue inciting antibiotics or other drugs
  - ⇨ Contact precautions and hand hygiene (water and soap are more effective than alcohol-based hand sanitizers in removing C. difficile spores, which are resistant to killing by alcohol.)
  - ⇨ **Initial drug** (regardless of severity)
    - **Fidaxomicin** (preferred): an oral macrolide antibiotic, 200 mg twice daily for 10 days. More safer, No dosage adjustment for renal or hepatic Impairment, however, use is limited by high cost and limited availability. Also preferred in recurrent episodes (<3 recurrence)

- **Oral vancomycin** (125 mg 4 times daily): The powder for injection may be diluted and used for oral.
- **Oral metronidazole** (if oral vancomycin and fidaxomicin are not available; used in addition to vancomycin if patients are refractory to monotherapy. Less effective for non-severe CD. Contraindicated in frail, age >65 years, and CD associated with inflammatory bowel disease)

⇨ **Recurrent episodes** (≥ 3 recurrence) → fecal microbiota transplantation followed by oral vancomycin.

⇨ **Fulminant colitis** (hypotension or shock, ileus, or megacolon): oral vancomycin plus IV metronidazole + surgical assessment

- **Prevention:** For patients at increased risk for recurrent CDI (age ≥65 years, history of severe CDI, or immunosuppression) who require ongoing antibiotics use → oral vancomycin (125 mg orally once daily) for the antibiotic duration plus one week after.

Tetanus

Caused by Clostridium tetani, anaerobic gram + rod, spore-forming, produces tetanospasmin toxin → tonic muscle spasms and and rigidity.

Transmission: direct contact in contaminated soil

Incubation period: 3 - 21 days.

Pathophysiology: Tetanospasmin toxin reaches the CNS through retrograde axonal transport → **cleaves a synaptobrevin protein** → prevention of inhibitory neurotransmitters (i.e., GABA and glycine) → tetanic spasms.

Features

- **Trismus**: lockjaw due to spasms of jaw musculature
- **Risus sardonicus**: sustained facial muscle spasm → raised eyebrows and grin (wide smile)
- **Opisthotonus**: backward arching of spine, neck, and head caused by spasms of the back muscles :spinal muscle spasms → backward arching of spine, head and neck.
- Dysphagia
- Laryngospasm and/or respiratory muscles spasms → respiratory failure
- Autonomic dysfunction: manifest early as irritability, restlessness, sweating, and tachycardia.

Diagnosis: Clinically = Muscle spasms and rigidity + Inadequate vaccination history. The wound is often unnoticed (the absence of a wound does not exclude tetanus).

Management

- **Supportive therapy**: e.g. ventilatory support, benzodiazepines and muscle relaxants
- **Wound cleaning and debridement**
- **Immunization**

⇨ Passive immunization → **Human tetanus immunoglobulin (HTIG):** Should be given to patients **with contaminated wounds** (**high-risk tetanus-prone wounds**) + Not completed 3 doses of tetanus vaccine, OR completed 3 doses, but last dose > 10 years ago, OR unknown vaccination history. (Clean and minor wounds do not require HTIG).

⇨ Active immunization →**Tetanus toxoid-containing vaccine (TT)**
- For **ANY** wound: if vaccination history is incomplete or unknown
- For contaminated wounds **ONLY:** if completed 3 doses, but the last dose > 10 years ago.

- **Antibiotics : Metronidazole is now preferred to benzylpenicillin as the antibiotic of choice** (500 mg intravenously every six to eight hours for 7 to 10 days).

Post-exposure tetanus prophylaxis

Previous doses of tetanus toxoid	Clean and minor wound		All other wounds	
	Tetanus toxoid-containing vaccine	Human tetanus immune globulin	Tetanus toxoid-containing vaccine	Human tetanus immune globulin
<3 doses or unknown	Yes	No	Yes	Yes
≥3 doses	Only if last dose given ≥10 years ago	No	Only if last dose given ≥5 years ago	No

Tetanus-prone wounds:
- contaminated puncture-type injuries
- wounds containing foreign bodies e.g. soil
- compound fractures
- wounds or burns with systemic sepsis
- certain animal bites and scratches
- wounds or burns that show extensive devitalised tissue
- wounds or burns that require surgery that is delayed > 6 hours.

Patients with large or dirty wounds + uncertain vaccination history → give tetanus toxoid vaccine + Human tetanus-specific immune globulin (HTIG).

Prevention: (only available in combination with other antigens)
- **DTap** ((**D**iphtheria/**T**etanus/**a**cellular **P**ertussis) vaccine: 5 doses before school-age, completed by 4-6 years of age
- **Tdap** (**T**etanus/low-dose **d**iphtheria/**a**cellular **p**ertussis) vaccine: booster vaccine at 11-12 years of age. Indicated at least once in adults who have never previously received a dose of Tdap. Pregnant women should receive Tdap during each pregnancy between 27 - 36 weeks of gestation, regardless of when the last dose was given.
- **Td** (**T**etanus/**d**iphtheria) vaccine: at 10-year intervals

Diphtheria

Caused by: *Corynebacterium diphtheriae*, a **gram positive rod**, non-spore-forming, anaerobic bacteria.

Transmission by: respiratory droplets

Incubation period: 2 - 5 days. The patients may be infectious for 4 weeks.

Pathophysiology

- **Diphtheria exotoxin** (composed of two chains: **chain B** (responsible for entry into host cells) & **chain A** (inhibits protein synthesis and causes cell death) → mucosal tissue necrosis → **greyish diphtheric membrane** on tonsils (may cause respiratory obstruction. Attempts to remove the pseudomembrane result in bleeding). Exotoxins may cause myocarditis or neurological defects.

Feature

- **Pharyngeal diphtheria** presents with: fever, sore throat, 'bulls neck' which results from cervical lymphadenopathy and mucosal swelling and adherent, grayish pharyngeal membrane which bleeds easily if irritated .
- **Cardiac involvement** → cardiomyopathy, myositis, arrhythmias.
- **Neurological involvement** → cranial neuropathies, and predominantly motor peripheral neuropathy
- **Cutaneous diphtheria:** presents with **non-healing ulcers covered with a grey membrane**, which can develop bacterial co-infection.

Diagnosis: Cultures from the throat and nose, including a portion of the membrane (if possible)

Treatment

- **Isolation,** secure a definitive **airway**, cardiac **monitoring**
- **Antibiotics:** (erythromycin or penicillin and possibly azithromycin)
- **Close contacts :** nasal and pharyngeal cultures + prophylactic antibiotic 7 to 10 day course of oral erythromycin (250 mg four times daily)

Listeria

Listeria monocytogenes is a gram positive bacillus. It has the unusual ability to multiply at low temperatures.

Transmission by: contaminated food, typically unpasteurised dairy products (eg, soft cheese)

Risk factors: **immunosuppressed** patients, **old age**, and **pregnant** women.

Features of listeriosis

- Gastroenteritis → diarrhoea
- Bacteremia
- Meningoencephalitis

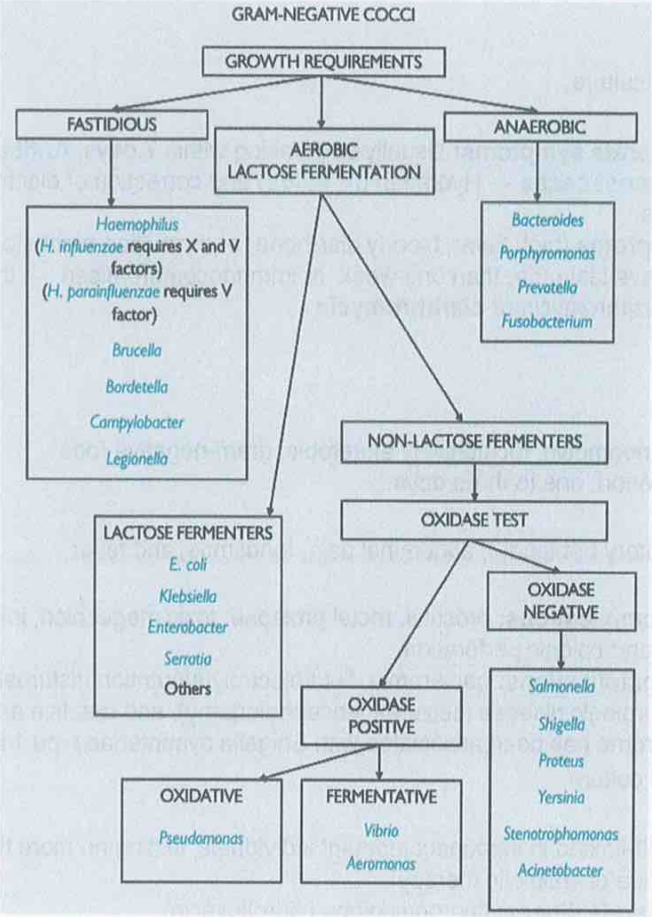
Diagnosis: **blood cultures**. **CSF** culture in meningoencephalitis

Management

- **CNS or bloodstream infection:** Ampicillin (2 g IV every 4 hours) or Penicillin G (4 million units IV every 4 hours) PLUS Gentamicin (5 mg/kg per day IV in 3 divided doses) for at least 2 weeks for bacteremia and 3 weeks for CNS infection. In penicillin-allergic patients → trimethoprim-sulfamethoxazole (TMP-SMX).
- **Gastroenteritis:** almost always self-limited in immunocompetent patients. For immunocompromised patients or older than age 65, → amoxicillin or TMP-SMX

> ***Listeria*** **meningitis should always be considered in patients with meningitis associated with brain stem involvement in elderly and immunosuppressed patients. The treatment of choice is gentamicin and ampicillin.**

Grame-negative bacteria



Campylobacter

Pathogenesis

- Campylobacter enteritis is an important cause of acute diarrhea worldwide. It is typically caused by Campylobacter jejuni or Campylobacter coli and is largely a foodborne disease

Transmission: by the faecal-oral route

Incubation period: 1-7 days.

Features

- Prodrome: headache, malaise
- Diarrhoea: often bloody
- Abdominal pain

Complications

- Guillain-Barre syndrome may follow *Campylobacter jejuni* infections
- Reactive arthritis
- Reiter's syndrome
- Septicaemia
- Endocarditis

Diagnosis: Stool culture

Management

- **Mild to moderate symptoms:** Usually self-limiting within 7 days. **Antibiotics are not needed for most cases** → Hydration (**IV fluids**) and correction of electrolyte abnormalities
- **Severe symptoms** (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week or immunocompromised. → the first-line antibiotic is azithromycin or **clarithromycin**

Shigella

Pathogenesis

- Shigella are nonmotile, facultatively anaerobic, gram-negative rods
- Incubation period: one to three days.

Features

- Diarrhea (watery or bloody), abdominal pain, tenesmus, and fever.

Complications

- **Intestinal complications:** proctitis, rectal prolapse, toxic megacolon, intestinal obstruction, and colonic perforation.
- **Systemic complications:** bacteremia, fluid/electrolyte/nutrition disturbances, leukemoid reaction, neurologic disease (seizures, encephalopathy), and reactive arthritis. hemolytic uremic syndrome has been associated with Shigella dysenteriae type 1 infection.

Diagnosis: Stool culture

Treatment

- Generally self-limited in immunocompetent individuals, lasting no more than seven days (in the absence of antibiotic therapy).
- **Mild to moderate illness:** fluoroquinolone (ciprofloxacin)
- **Severe disease** (characterized by bacteremia, intestinal or extraintestinal complications, or need for hospitalization) or immunocompromised: carbapenem (such as ertapenem, imipenem, or meropenem)

Escherichia coli

Pathogenesis

- *E.coli* is **Gram-negative rod,** anaerobic, lactose-fermenting, normal gut commensal, induces diarrhoeal illnesses and UTIs

Strains & Features

- ***Enterotoxigenic E. coli (ETEC)*** *→ Watery diarrhoea (through plasmid-encoded toxin production)*
- ***Enteroinvasive E. coli (EIEC)*** *→ Dysentery*
- **Enterohemorrhagic E. coli (EHEC): *E. coli* O157:H7**
  - ⇨ **Producing Shiga toxin**
  - ⇨ **Associated with** severe, haemorrhagic, watery diarrhoea → high mortality rate
  - ⇨ **Complicated by** haemolytic uraemic syndrome.
  - ⇨ **Spread by** contaminated ground beef.

Diagnostic test: Stool culture on sorbitol-MacConkey medium

Treatment

- **Supportive care** (fluid, electrolyte, and nutrition)
- **Most cases of diarrhoea associated with E. coli resolve spontaneously**
- **In patients with severe, bloody, or persistent diarrhoea** → azithromycin or ciprofloxacin
- **Antibiotic therapy is not recommended in cases of Shiga toxin-producing E. coli infection** because of the association with hemolytic uremic syndrome
- **Multiple drug resistant *Escherichia coli* :**
  - ⇨ **Mechanism of resistance → Extended spectrum beta-lactamase (ESBL) production** → inactivates penicillins and cephalosporins
  - ⇨ **Treatment:** carbapenems (**first line**)

Salmonellae

Pathogen: Gram-negative rods grow under both aerobic and **anaerobic** conditions.

Incubation period: 5–30 days

Transmission: fecal-oral, through contaminated food or water. Humans are the only reservoir for S. Typhi and S. Paratyphi A.

Diseases causes by Salmonella: gastroenteritis, enteric fever, bacteremia, and osteomyelitis.

Risk factors: travel to endemic regions, poor sanitation, contact with a known typhoid case or carrier.

Classification

- **Typhoidal Salmonella,** such as Salmonella Typhi or Salmonella Paratyphi, primarily colonizes humans. It is transmitted via the consumption of fecally contaminated food or water and causes a systemic illness, usually with little or no diarrhoea.

- **Nontyphoidal Salmonella**:
  - ⇨ **Salmonella gastroenteritis**:
    - **Features:** common causes of foodborne gastroenteritis, particularly in outbreak settings. Commonly associated with poultry and eggs. Symptoms typically occur within 8 to 72 hours following exposure → diarrhoea, nausea, vomiting, fever, and abdominal cramping
    - **Treatment:**
      - 🕮 **Mild to moderate illness:** Supportive care. Antibiotics are not routinely recommended → increase the risk of extended asymptomatic Salmonella carriage and do not shorten the duration of illness.
      - 🕮 **Severe illness** (severe diarrhoea, high or persistent fever, need for hospitalisation) or at high risk for invasive disease (>50 years, immunosuppression, atherosclerotic disease, prosthetic heart valves, or prosthetic joints.) → azithromycin, trimethoprim-sulfamethoxazole or cefixime.
  - ⇨ **Bacteremia & Extraintestinal infections**
    - **Endovascular infection:** affects atherosclerotic sites of large vessels, most commonly abdominal aorta (especially infrarenal aorta) →, subacute fever, abdominal pain, and back pain.
    - **Salmonella osteomyelitis:** occurs more commonly in children (especially those with hemoglobinopathies) and typically involves the epiphyses of long bones.
    - **Treatment:** 3rd generation cephalosporin (ceftriaxone or cefotaxime), fluoroquinolone (ciprofloxacin or levofloxacin), or both in severe infections.
  - ⇨ Blood and bone **infections caused by non-typhi salmonella (NTS) are typically associated with malaria and homozygous sickle cell disease**. Salmonella enteritidis and S. typhimurium are the most common.

Enteric (Typhoid and paratyphoid) fever

Types

- *Salmonella typhi* causes typhoid
- *Salmonella paratyphi* (types A, B & C) causes paratyphoid

Features

- Initially systemic upset (headache, fever, chills and arthralgia)
- Relative bradycardia, pulse-temperature dissociation
- **Abdominal pain, distension**
- **Diarrhoeal disease:** mild yellow-green diarrhea, comparable to pea soup (caused by purulent, bloody necrosis of the Peyer patches)
- **Constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid** (as a result of swollen Peyer patches in the ileum)
- **Rose spots** (faint salmon-colored macules on the trunk and abdomen)
- **Neurological symptoms** (delirium, coma)
- Hepatosplenomegaly

Complication

- **Chronic Salmonella carrier**
  - ⇨ **Definition:** positive stool cultures 12 months after overcoming the disease. gallbladder may act as a reservoir of infection and cause relapse.
  - ⇨ **Incidence:** up to 6% of the patients become chronic carriers. More common in females and patients with cholelithiasis
  - ⇨ **Presentation:** typically asymptomatic
  - ⇨ **Treatment:** fluoroquinolones (e.g., ciprofloxacin) administered for at least 1 month
  - ⇨ Chronic carriers are not allowed to work in the food industry.
  - ⇨ Increased risk for cholangiocarcinoma (bile duct cancer)
- **Intestinal perforation** leading to peritonitis.
- Rarely causes sepsis, meningitis, myocarditis, and renal failure

Investigations

- Anemia, **leukopenia**, leukocytosis, and abnormal liver function tests.
- **Cultures:** from blood, stool, urine, rose spots, duodenal contents, or bone marrow, but most cultures are not highly sensitive. **Bone marrow is the most sensitive culture** but is invasive and usually not warranted. **Diagnosis often made presumptively on the basis of a febrile illness without other explanation.**
- **Serology (Widal test):** poor sensitivity, negative in early infection. In endemic areas because positive results may represent previous infection.

Treatment

- **Resistance** to fluoroquinolones has become a major problem worldwide. Most Salmonella Typhi and Salmonella Paratyphi remain susceptible to azithromycin and third-generation cephalosporins.
- **Severe or complicated disease** (systemic toxicity, depressed consciousness, prolonged fever, organ dysfunction, or hospitalized patients)
  - ⇨ 1st line → ceftriaxone
  - ⇨ If there is suspicion for ceftriaxone resistance → carbapenem (eg, meropenem)
  - ⇨ For patients with severe systemic illness (delirium, stupor, coma, or shock) → add dexamethasone (3 mg/kg followed by 1 mg/kg every 6 hours for 48 hours)
- **Uncomplicated disease**
  - ⇨ Ciprofloxacin
  - ⇨ If there is suspicion for ciprofloxacin resistance → azithromycin
- **In pregnancy: the drug of choice is parenteral ceftriaxone.**

Prevention

- **Typhoid vaccine** in endemic areas. provides 50% protection. It does not protect from paratyphoid infection.
  - ⇨ parenteral (Typh-I): inactivated vaccine (i.e. killed)
  - ⇨ oral (Typh-O): **live-attenuated vaccine**

Bacterial organism and antibiotic choice

Organism	Effective drug
Gram-positive cocci (Staphylococcal & streptococcal)	➲ Penicillins (oxacillin, cloxacillin) ➲ piperacillin/tazobactam ➲ new fluoroquinolones (moxifloxacin, levofloxacin, and gemifloxacin)
Methicillin-resistant Staphylococcus aureus (MRSA)	➲ Vancomycin ➲ Teicoplanin ➲ Ceftaroline (3rd generation ceftriaxone, the only ceftriaxone to cover MRSA)
Vancomycin-resistant enterococci	➲ Quinupristin/dalfopristin
Anaerobic infection	➲ Metronidazole (the most active agent). ➲ Carbapenems (imipenem, meropenem): equal to metronidazole ➲ beta-lactam/beta- lactamase combination (piperacillin/tazobactam, ampicillin/sulbactam, or amoxicillin/clavulanate)
Pseudomonal infection (hospital-acquired)	➲ piperacillin with tazobactam ➲ ceftazidime ➲ Carbapenems (imipenem, meropenem) ➲ ciprofloxacin (the only Quinolone will reliably cover Pseudomonas
gram-negative bacilli, but not Pseudomonas	➲ Ampicillin/sulbactam ➲ Amoxicillin/clavulanate ➲ 3rd & 4th generation cephalosporins (ceftriaxone, cefotaxime)
gram-negative bacilli including Pseudomonas	➲ Only cephalosporin will cover Pseudomonas: ceftazidime & cefepime
Enterobacteriaceae, such as E. coli, Proteus, Enterobacter, Haemophilus, Moraxella, Citrobacter, Morganella, Serratia, and Klebsiella.	➲ Quinolones (ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin) ➲ Carbapenems (imipenem, meropenem)
Mycoplasma, Chlamydia, and Legionella.	➲ new fluoroquinolones (moxifloxacin, levofloxacin, and gemifloxacin)

When selecting antibiotics, first consider three factors

1. the patient (allergy, renal and hepatic function, severity of illness e.g. life-threatening sepsis , and, if female, whether pregnant)
2. the known or likely causative organism and its antibacterial sensitivity
3. the risk of bacterial resistance with repeated courses (previous or current culture with resistant bacteria. risk of treatment failure in patient who have had repeated antibacterial courses . In patients receiving antibacterial prophylaxis, an antibacterial from a different class should be used.)

Meningitis

Category	Details
Definition	Life-threatening infection causing inflammation of the meninges (brain and spinal cord membranes).
Causes	**2-50 years:** Neisseria meningitidis, Streptococcus pneumoniae **>50 years:** S. pneumoniae, N. meningitidis, Listeria monocytogenes **Immunocompromised:** Listeria monocytogenes
Most Common Viral Cause	Coxsackievirus (an enterovirus)
Key Bacterial Causes	Streptococcus pneumoniae (>50% cases), N. meningitidis (with diagnostic petechial rash)
Partially Treated Meningitis	Antibiotic treatment may yield false-negative CSF cultures and Gram stains but not affect WBC counts.

Clinical Features

Category	Details
Classic Triad	Fever, nuchal rigidity, altered mental status (found in <50% of patients).
Signs of Meningeal Irritation	Neck stiffness, Kernig sign, Brudzinski sign, jolt accentuation of headache.
Pathogen-Specific Symptoms	**N. meningitidis:** Petechial/purpuric rash, Waterhouse-Friderichsen syndrome **Viral:** Flu-like symptoms, rash
Raised Intracranial Pressure	Cranial nerve palsies, papilledema.
Complications	Septicemia, deafness (common in pneumococcal meningitis).

Signs of meningeal irritation

Sign	Positive test
Kernig sign	When the patient is lying supine with the hip flexed at 90 degrees, attempt to extend the leg at the knee → Resistance to extension at the knee or pain in the lower back or posterior thigh.
Brudzinski sign	When the patient is lying supine, passive flexion of the head toward the chest → Flexion of the knees and hips.
Jolt accentuation of headache	When the patient rotates the head horizontally two to three times per second → exacerbation of headache

Diagnostic Tests

Test	Findings
Lumbar Puncture (CSF Analysis)	**Gold standard test:** cloudy/purulent fluid in bacterial meningitis, clear in viral.
Blood Cultures	Positive in 50-90% of cases.
CT Brain	Recommended before LP if seizures, papilledema, altered consciousness, or immunosuppression are present.
CXR	Useful for detecting TB-related meningitis.

Indications for imaging before LP = LP FAILS

- **To remember the indications for imaging before LP, think of LP FAILS:** **Focal neurological deficits, Altered mental status, Immunocompromised or ^ ICP, Lesions (space-occupying lesions in the brain), Seizures.**

CSF Analysis in Meningitis

Cerebrospinal fluid analysis in meningitis			
	Normal	**Bacterial meningitis**	**Viral meningitis**
Appearance	Clear fluid	Cloudy, purulent fluid	Clear fluid
Cell count	Cell count < 5/mm3	Pleocytosis (WBC > 1000/mm3) with ↑ Granulocytes (> 80%)	Variable cell count (WBC 10–500/mm3) with ↑ Lymphocytes
Opening pressure	5–18 cm H_2O	High	Normal or High
Protein	15–45 mg/dL	High (> 1 g/l)	Normal or raised
Glucose	40–75 mg/dL	Low (< 1/2 plasma)	Normal
Gram stain and culture	No organisms	**Positive gram stain and culture** ➲ Meningococci: gram-negative diplococci ➲ Pneumococci: gram-positive diplococci ➲ Listeria: gram-positive rods ➲ Haemophilus influenzae: gram-negative coccobacilli	No organisms
Tuberculous meningitis: Similar to other bacterial meningitis except of (clear or slight cloudy fluid with a spiderweb clot + predominantly ↑lymphocytes count)			

Causes of raised CSF lymphocytes & proteins

Conditions associated with raised lymphocytes	Conditions associated with raised protein
➲ Viral meningitis/encephalitis ➲ TB meningitis ➲ Partially treated bacterial meningitis ➲ Lyme disease ➲ Behcet's, SLE ➲ Lymphoma, leukaemia	➲ Tuberculous, fungal and bacterial meningitis ➲ Viral encephalitis ➲ Guillain-Barre syndrome ➲ Spinal block (Froin's syndrome): ↑CSF protein below a spinal canal blockage (e.g. tumour, disc, infection)

Treatment: Empiric Antibiotics

Patient Characteristics	Empiric Antibiotics
Age 2-50 years	Vancomycin + Ceftriaxone/Cefotaxime
Age >50 years	Vancomycin + Ampicillin + Ceftriaxone/Cefotaxime
Immunocompromised	Vancomycin + Ampicillin + Cefepime/Meropenem

Adjunctive Therapy:

- Dexamethasone (0.4 mg/kg every 12 hours for 4 days) with the first dose of antibiotics for pneumococcal meningitis.
- **Acyclovir** for viral meningoencephalitis.
- **Steroids** for TB meningitis.

Specific antimicrobial therapy (after culture & sensitivity result)

Pathogen-specific therapy in meningitis	
Pathogen	**Examples of antimicrobial agents**
S. pneumoniae (penicillin-resistant strains)	Vancomycin
MRSA	
S. epidermidis	
H. influenzae	Third-generation cephalosporin (e.g., cefotaxime OR ceftriaxone
S. pneumoniae (penicillin-susceptible strains)	
N. meningitidis	
E. coli	
L. monocytogenes	• Ampicillin • Consider the addition of gentamicin.
S. agalactiae	
Enterococcus spp.	• Gentamicin • PLUS either ampicillin OR vancomycin
P. aeruginosa	Cefepime
R. rickettsii	Doxycycline

Management of Contacts

- **Indications:** Close contacts of meningococcal meningitis patients. Pneumococcal meningitis usually does not require prophylaxis unless in clusters.
- **Antibiotics:** Ciprofloxacin (single oral dose) or Rifampin (twice daily for two days).
- **Vaccination:** Meningococcal vaccination for contacts when serotype results are available.

Complications

Complication	Details
Hearing loss	Common with pneumococcal meningitis (up to 50% cases).
Septicemia	Risk with meningococcal infections.

Partially Treated Bacterial Meningitis

- **Definition:** Bacterial meningitis treated inadequately due to missed diagnosis or incomplete antibiotic course, leading to diagnostic challenges.
- **Affected Parameters:**
  - **CSF Gram stain:** ↓ Positivity to < 60%, may appear negative.
  - **CSF culture:** ↓ Bacterial growth, particularly meningococcus.
- **Unaffected Parameters:**
  - CSF glucose, protein, neutrophils, bacterial antigen tests, and PCR remain unaffected.
  - White cell count stays elevated; a normal count makes the diagnosis unlikely.

Do not delay empiric antibiotic therapy in patients suspected of bacterial meningitis. **Start empiric antibiotics immediately after obtaining blood cultures and CSF samples. If LP is delayed for any reason (e.g., the need for a CT or hemodynamic stabilization), obtain blood cultures and administer antibiotics until it can be performed.**

Ampicillin is added if patients are at risk of Listeria spp. infection (e.g., pregnant women, adults > 50 years of age, or immunocompromised patients) because cephalosporins are ineffective against Listeria spp.

Acyclovir should be started in all patients who present with typical clinical signs of viral meningoencephalitis and only discontinued after PCR and antibody tests are negative for HSV and VZV, even if CSF is initially normal.

Fungal meningitis

- **Causes:** candida, Cryptococcus neoformans (Cryptococcus meningoencephalitis)
- **Risk factors:** immunocompromised, inserted ventricular devices
- **Clinical course:** subacute onset with (low) fever, fatigue, and headaches. Meningeal symptoms are often absent.
- **Diagnosis:**
  - ⇨ elevated CSF opening pressure, CSF **beta-D-glucan assay (detect systemic fungal infection)** and CSF culture.
  - ⇨ Cryptococcal antigen testing of CSF and serum
  - ⇨ Brain MRI: gelatinous pseudocysts (soap bubble appearance)
- **Treatment:**
  - ⇨ amphotericin B (5 mg/kg IV once daily) with or without flucytosine (25 mg/kg orally four times daily) for few weeks followed by oral fluconazole.
  - ⇨ Infected ventricular devices should be removed.

Viral encephalitis

Definition: encephalitis is an inflammation of the brain parenchyma

Causes

- The most common cause is **herpes simplex,** usually **type I** (HSV-1).
- **West Nile virus** (the most common cause of viral encephalitis in the US). Diagnosed by IgM antibodies in the serum or CSF.
- Cytomegalovirus (CMV), Epstein-Barr virus (EBV) : most common in immunocompromised or HIV-positive individuals.
- Other viruses: respiratory viruses, human herpes virus 6 (HHV6), rubella, or mumps, **measles**, varicella zoster, enteroviruses and rabies.

Features

- Altered mental status with fever and headache is the primary clue to the diagnosis.
- Symptoms and signs of meningeal irritation (photophobia and nuchal rigidity) are usually absent in pure encephalitis but often accompany meningoencephalitis.
- Seizures and focal neurologic deficit (eg, hemiparesis, cranial nerve palsies)
- Clues on physical examination
  - ⇨ **Temporal lobe signs** e.g. aphasia, strongly suggests **Herpes simplex encephalitis**
  - ⇨ **Parotitis** strongly suggests mumps encephalitis
  - ⇨ **Grouped vesicles in a dermatomal pattern** may suggest varicella zoster virus (VZV).
  - ⇨ **Flaccid paralysis**, a polio-like presentation, strongly suggests the **West Nile virus** infection (a maculopapular rash seen in 50% of cases): may be misdiagnosed as Guillain-Barré syndrome.
  - ⇨ **Hydrophobia, aerophobia, pharyngeal spasms, and hyperactivity** suggest encephalitic rabies.

Investigations

- **Brain CT/MRI**
  - ⇨ CT is useful to rule out space-occupying lesions. MRI is sensitive for detecting demyelination (e.g., acute disseminated encephalomyelitis [ADEM] or progressive multifocal leukoencephalopathy [PML]).
  - ⇨ Temporal lobe involvement is strongly suggestive of herpes simplex virus (HSV) encephalitis,
  - ⇨ Thalamus or basal ganglia involvement may be observed in the setting of encephalitis due to respiratory viral infection, Creutzfeldt-Jakob disease, arbovirus, and tuberculosis.
  - ⇨ Hydrocephalus may suggest nonviral etiologies such as bacteria, fungal, or parasitic.
- **Lumbar puncture (LP) for cerebrospinal fluid (CSF) analysis for:**
  - ⇨ **Cell count, glucose, and protein:** viral encephalitis → ↑ WBC count (but < 250/mm3) with lymphocytes predominance + ↑ protein (but <150 mg/dL) + normal glucose (>50% of blood value): HSV, mumps may →↓glucose.
  - ⇨ **CSF polymerase chain reaction (PCR):** for herpes simplex virus (HSV)-1, HSV-2, VZV, and enteroviruses. **It is the diagnostic test of choice.**
  - ⇨ **CSF viral culture:** for rare causes (eg, influenza, parainfluenza, measles, mumps) for which PCR testing is unavailable.
  - ⇨ **Serology** (most important for patients with negative PCR and not improving): for arboviruses, HIV testing, IgM serology for West Nile virus, Epstein-Barr virus
- **Electroencephalography (EEG):** often abnormal in acute encephalitis. Focal temporal lobe abnormality is suggestive of HSV encephalitis.

CSF findings: viral encephalitis vs bacterial meningitis:

- **Viral encephalitis: ↑ WBC count (but < 250/mm3) with lymphocytes predominance + ↑ protein (but <150 mg/dL) + normal glucose (>50% of blood value): HSV, mumps may →↓glucose.**
- **Bacterial meningitis: ↑ WBC count (>2000/mm3) with neutrophil predominance + ↑protein (>200 mg/dL) + hypoglycorrhachia (↓ glucose).**

Treatment

- Start immediate antiviral therapy with acyclovir for all patients with suspected viral encephalitis

Initial therapy for viruses that cause encephalitis

Virus	Specific therapy
Herpes simplex OR Varicella-zoster	Acyclovir
Cytomegalovirus	Ganciclovir plus foscarnet
Human herpesvirus 6	Gancyclovir or foscarnet
Human immunodeficiency virus	Antiretroviral therapy
Influenza	Oseltamivir
JC virus	Reversal of immunosuppression if possible
Measles	Ribavirin
St. Louis encephalitis	Interferon-2 alpha
Epstein-Barr	No specific treatment
West Nile	No specific treatment

Differential diagnosis

Anti-NMDAR antibodies is the most common cause of autoimmune encephalitis

- **Autoimmune encephalitis:**
  - ⇨ **Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (anti-NMDA encephalitis)**
    - **The most common cause of autoimmune encephalitis**
    - **Mechanism:** Antibodies against neuronal cell-surface proteins
    - It may or may not be associated with cancer.
    - may be associated with ovarian teratoma
  - ⇨ **Paraneoplastic encephalitis**
    - **Mechanism: Antibodies against intracellular neuronal proteins**
    - Almost always associated with cancer (high cancer association)
    - **Subtypes**
      - 🕮 **Anti-Hu antibodies** encephalomyelitis: associated with small cell lung cancer (SCLC)
      - 🕮 **Anti-Yo antibodies:** associated with gynecological and breast malignancies
  - ⇨ **Diagnosis:** Neuroimaging, EEG, lumbar puncture, CSF and serum neuronal antibody testing (e.g., anti-Hu antibodies, anti-NMDAR antibodies)
  - ⇨ **Treatment:** high-dose glucocorticoids plus either IVIG or therapeutic plasma exchange (TPE)
- **Limbic encephalitis**
  - ⇨ **Caused by auto-antibodies directed against antigens richly expressed in the limbic system**
  - ⇨ **Most commonly associated with small cell lung carcinoma (SCLC)**
  - ⇨ **Features:** severe short-term memory impairment, seizures, confusion, psychiatric symptoms (e.g., depression, hallucinations, anxiety)
  - ⇨ **Diagnosis:**
    - MRI shows hyperintense abnormalities in the medial aspect of the temporal lobes.
    - CSF and serum neuronal antibody: **anti-Hu antibody is present in about 50**
  - ⇨ **Management:** treatment of primary tumor and immunotherapy

Diagnostic criteria for possible autoimmune encephalitis

All three of the following criteria must be met:

1) **Subacute onset (rapid progression of <3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms**
2) **At least one of the following:**
   - **New focal CNS findings**
   - **Seizures not explained by a previously known seizure disorder**
   - **CSF pleocytosis (>5 white blood cells per mm3)**
   - **MRI features suggestive of encephalitis**
3) **Reasonable exclusion of alternative causes**

Herpes simplex encephalitis (HSE)

HSE: behavioral changes and CT/MRI brain showing temporal lobe changes

Causes

- **Herpes simplex type 1** (HSV-1) responsible for 95% of cases in adults & older children. Characteristically affects the temporal lobes → **temporal lobe signs** e.g. aphasia.
- **Herpes simplex type 2** (HSV-2): almost exclusively seen in neonates who acquire the virus during delivery. characterised by generalised brain involvement.

Features

- Fever, headache, vomiting
- **Psychiatric symptoms**, **seizures**, focal features e.g. aphasia or **alteration in consciousness**

Investigation

- Lumbar puncture for CSF analysis: **lymphocytosis**, elevated protein, mildly raised red cells and a normal or low glucose.
- **PCR for HSV DNA in CSF** is a highly specific test (**the gold standard for the diagnosis.)**
- **MRI brain:** demonstrate temporal lobe changes & eliminate other alternative causes of mental status changes such as brain abscess.
- **EEG pattern: lateralised periodic discharges at 2 Hz**

Treatment

- Intravenous aciclovir (10 mg/kg every 8 hours): Started immediately on clinical suspicion - do not wait for confirmation. Continued until CSF PCR is negative, or for at least 14 days.

Progressive multifocal leukoencephalopathy (PML)

Definition

- Progressive multifocal leukoencephalopathy (PML) is a **demyelinating disease** which results from the **reactivation** of John Cunningham virus (JC virus) infecting **oligodendrocytes** in patients with **compromised immune systems**.

Risk factors

- **Advanced HIV/AIDS** (with CD4 counts of less than 100)
- **Treatment with Natalizumab**

> **Three risk factors predispose patients with multiple sclerosis to PML:**
> 1. **positive anti-JC viral serum antibodies**
> 2. **prior use of immunosuppressants, and**
> 3. **increased duration of natalizumab treatment and its number of infusions (25-49 infusions).**

Features: subacute onset

- Altered mental status, behavioural changes,
- Speech, motor, visual impairment
- Ataxia, Head tremor
- Motor deficits: Focal neurology progressing over a period of months to paresis and even coma.
- Seizures

Diagnosis

- CT: single or multiple lesions, **no mass effect**, **don't usually enhance**.
- MRI is better - **high-signal demyelinating white matter lesions**
- **CSF PCR for the JC virus.**
- **Brain biopsy**: **the definitive diagnostic test** (showing asymmetric foci of demyelination and intranuclear inclusions containing the JC virus).

Treatment

- No effective treatment, but progression can be slowed by immune reconstitution (by initiation of antiretroviral therapy in HIV or withdrawn of immunosuppressive medications)

Differential diagnosis

- **New demyelinating lesions in patients with multiple sclerosis:** early in the disease MS and PML may appear similar. Periventricular location or well-defined borders favor new MS lesions
- **HIV/AIDS encephalopathy:** often diffuse white matter disease, with atrophy, symmetric, spares the subcortical U-fibers
- **cerebral toxoplasmosis:** usually enhance
- **immunodeficiency-associated CNS lymphoma:** usually enhance

Sepsis

Definition

- **Sepsis:** a severe, life-threatening infection causing organ dysfunction (≥ 2 in SOFA score). The Sequential Organ Failure Assessment (SOFA) or Quick SOFA (qSOFA) includes 1 point for each of 3 criteria:
  1. Altered GCS
  2. Respiratory rate > or equal to 22/min
  3. Systolic blood pressure ≤100mmHg

- **Septic shock:** persisting hypotension requiring vasopressors to maintain a mean arterial pressure of ≥ 65 mm Hg **and** a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation.

Risk factors

- Age (< 1 year and > 75 years)
- Comorbidities (diabetes mellitus, cirrhosis, splenectomy, sickle cell disease, alcohol use disorder)
- Immunosuppression (neutropenia, corticosteroid, chemotherapy, immunosuppressant treatment)
- Intensive care or prolonged admission (nosocomial infections)
- Invasive medical devices (e.g., endotracheal tubes, intravenous lines, urinary catheters)

Complications

- Multiple organ failure
- Disseminated intravascular coagulation (DIC)

Management

- **Initial investigations**
  - ⇨ Obtain IV access and blood samples including 2 sets of blood cultures and serum lactate.
  - ⇨ Complete evaluation for organ dysfunction, e.g., CBC, CRP, blood glucose, RFT, electrolytes, LFT, blood gas, coagulation panel
  - ⇨ Consider additional imaging and cultures (urine, wound, sputum) based on clinical suspicion. **Positive cultures are not mandatory for the diagnosis of sepsis.**
- **Supportive care**, e.g., treating hypotension, respiratory support as needed, maintenance of normoglycemia, nutritional support.
  - ⇨ Initiate fluid resuscitation with 30 mL/kg of crystalloid fluid.
  - ⇨ Add vasopressors if shock persists despite adequate fluid resuscitation. Norepinephrine is the 1st line
- **Start empiric broad-spectrum antibiotics** (within 1 hour in septic shock).
  - ⇨ If the source of infection is clear → administer antibiotics that cover the most common causative pathogens.
  - ⇨ Unclear source of infection → empiric antibiotic
- **Control of sepsis source**, e.g., remove infected intravascular catheters, consult surgery for acute abdomen
- **Identify and treat complications**, e.g., DIC, ARDS, AKI
- **VTE prophylaxis**
- **Corticosteroids** (hydrocortisone) for patients with risk of adrenal crisis.

Do not rely on fever or hypothermia to rule sepsis either in or out. Some people may not develop a fever, e.g. (older or very frail, severely ill), people having cancer treatment.

Tuberculosis (TB)

Definition:

TB is an infectious disease caused by *Mycobacterium tuberculosis* affecting the lungs primarily but also spreading to other parts of the body.

Pathophysiology:

- Infection occurs via inhalation of airborne droplets containing *Mycobacterium tuberculosis*.
- Primary infection leads to either clearance, latent TB, or active disease.
- Reactivation of latent TB occurs primarily in immunocompromised individuals.

Clinical Features:

- **Pulmonary TB:** Chronic cough, hemoptysis, night sweats, weight loss, fatigue.
- **Extrapulmonary TB:** Involvement of lymph nodes, CNS (meningitis), bones (Pott's disease), and other organs.
- **Miliary TB:** Disseminated TB involving multiple organs.

Diagnosis:

1. **Screening Tests:**
    - Tuberculin skin test (TST) or Interferon-Gamma Release Assays (IGRAs).
2. **Definitive Diagnosis:**
    - **Sputum microscopy** (Acid-fast bacilli).
    - **Nucleic acid amplification tests (NAATs)** for quick confirmation.
    - **Culture** (gold standard but slow).
3. **Imaging:**
    - Chest X-ray or CT showing upper lobe consolidation, cavitation, or lymphadenopathy.

Treatment:

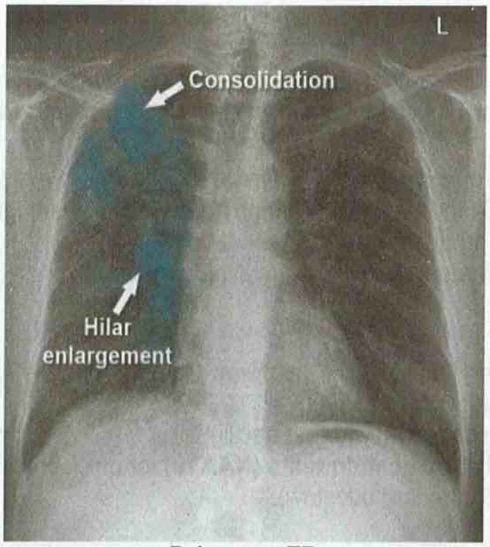
- **Standard regimen for drug-sensitive TB:**
    - **Initial phase:** 2 months of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol (RIPE).
    - **Continuation phase:** 4 months of Rifampicin and Isoniazid.
    - **Adjuvant:** Pyridoxine (vitamin B6) to prevent peripheral neuropathy from Isoniazid.
- **Drug-resistant TB:** Requires longer courses with second-line drugs (e.g., bedaquiline, linezolid).
- **Extrapulmonary TB:** Treated similarly, but CNS TB requires a longer course (up to 12 months) with corticosteroids.
- **Length of treatment:**
    - All non-CNS TB (e.g., pulmonary TB, bone TB): 6-month course (2 months of quadruple therapy, 4 months of dual therapy.
    - TB meningitis: 12 months
- **Tuberculous pleural effusion:** Anti-TB + drainage (with large effusions causing breathlessness) + corticosteroids to delay reaccumulation.

Complications:

- Chronic lung disease (bronchiectasis, fibrosis).
- Pleural effusion.
- Spread to other organs (CNS, lymph nodes, bones).
- Drug resistance.

Prevention:

- **BCG vaccine:** Administered to children in high-risk areas.
- **Screening and treatment** of latent TB in high-risk groups.
- **Isolation protocols:** For active pulmonary TB until non-infectious.



Pulmonary TB

Antituberculous drugs: Actions & side-effects

Drug	Mechanism of Action	Side Effects	Special Considerations
Rifampicin	Inhibits bacterial DNA-dependent RNA polymerase, preventing transcription	- Hepatotoxicity (elevated bilirubin) - Cytochrome P450 inducer → interactions with HIV antiretrovirals - Orange discolouration of body fluids - Thrombocytopenia, acute interstitial nephritis - Interacts with oral contraceptives, causing failure	- Preferred replacement in HIV patients: **Rifabutin** or **Rifapentine** (less P450 interaction) - No dose adjustment required in renal failure
Isoniazid	Inhibits mycolic acid synthesis, disrupting bacterial cell wall	- Hepatotoxicity (most common) - Vitamin B6 deficiency (peripheral neuropathy, sideroblastic anemia) - Drug-induced lupus - CNS toxicity (seizures, psychosis)	- Prophylaxis: **Pyridoxine (B6)** 25–50 mg/day - Toxicity treatment: High-dose pyridoxine - Dose adjustment not required in renal failure

Drug	Mechanism of Action	Side Effects	Special Considerations
Pyrazinamide	Converted to pyrazinoic acid, inhibiting fatty acid synthase	- Hepatotoxicity (highest risk) - Hyperuricemia → gout - Arthralgia - Photosensitivity	- Avoid in severe liver disease - No dose adjustment needed in renal impairment
Ethambutol	Inhibits arabinosyl transferase, disrupting mycobacterial cell wall (bacteriostatic)	- Optic neuritis (red-green colour blindness) - Hyperuricemia	- **Visual acuity monitoring** during treatment - Dose adjustment needed in renal impairment to prevent toxic effects

INH Injures Neurons and Hepatocytes

All hepatotoxic antituberculous drugs should be discontinued if:

- **Serum bilirubin ≥3 mg/dL or serum transaminases >5 times the upper limit of normal**
- **Symptoms of hepatitis (abdominal pain, nausea, vomiting, fatigue or jaundice) + serum transaminases >3 times the upper limit of normal.**

When all antituberculous drugs are discontinued due to hepatotoxicity:

- **If the patient is not severely ill and not infectious (smear-negative) → No treatment until LFTs improves.**
- **If clinically unwell or sputum smear is positive within two weeks of starting treatment → consider three drugs not associated with hepatoxicity (ethambutol, a fluoroquinolone (levofloxacin or moxifloxacin), and streptomycin) until LFT improves.**
- **Once LFT improves → reintroduce the drugs sequentially in order of isoniazid, rifampicin and pyrazinamide with daily monitoring of LFT.**

Latent tuberculosis infection (LTBI)

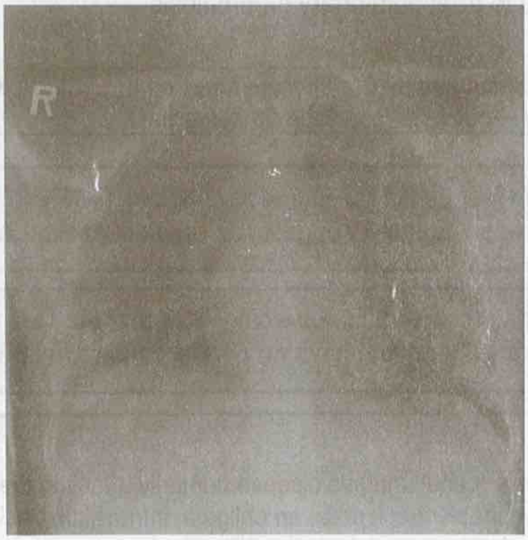
Aspect	Details
Definition	A positive screening test for *M. tuberculosis* (TST or IGRA) with no evidence of active TB on radiology.
Epidemiology	- 30% of exposed individuals develop LTBI - Lifetime risk of reactivation: 5–10%
Risk Factors	- Close contact with TB patients - Immunosuppression (HIV, transplant recipients) - Living or traveling to high-TB prevalence regions
Screening Indications	- All HIV patients - Before starting immunosuppressive therapy - Recent close contact with TB cases
Diagnosis	**Screening tests** - **Mantoux Tuberculin Skin Test (TST)**: Can be positive due to TB infection or BCG vaccination. Positive if induration ≥ 5 mm. - **IGRA Test**: Measures IFN-γ response to TB antigens. Useful for those vaccinated with BCG, but cannot differentiate active from latent TB. **Radiology** - Chest X-ray: No TB-related changes. (e.g., no hilar lymphadenopathy or cavitation)
Interpretation of TST Results (measure the induration, not surrounding erythema)	▫ <5 mm: Negative (vaccinate if unvaccinated) ▫ 5–15 mm: Positive (due to TB infection, BCG, or atypical mycobacteria) ▫ >15 mm: Strongly positive (highly suggestive of TB, requires chest X-ray)
Pre-treatment Tests	- Check liver function, HIV, and hepatitis B and C status before initiating treatment
Treatment Regimens	1. **Isoniazid (INH)**: 300 mg/day for 6–9 months (with pyridoxine to prevent neuropathy) 2. **Rifampin (RIF)**: 600 mg/day for 4 months 3. **INH + Rifapentine**: Weekly for 3 months (**preferred**)
Complications	Reactivation of latent TB, especially in immunocompromised individuals.

In immunocompromised (HIV and CD4 < 200 cells/mm3, or after transplant) → Interferon-gamma release assay and a concurrent Mantoux test:

- ➔ **If either test is positive → assess for active TB.**
- ➔ **If assess for active TB is negative → treatment for latent TB infection.**

Miliary Tuberculosis (TB)

Aspect	Details
Definition	A severe form of TB with hematogenous spread causing widespread granulomas in multiple organs.
Pathophysiology	Dissemination of *Mycobacterium tuberculosis* through the bloodstream, forming granulomas in the lungs, liver, spleen, CNS, and bone marrow.
Risk Factors	HIV, immunosuppression (post-transplant, chemotherapy), malnutrition, lung disease, children, elderly
Clinical Features	Fever, night sweats, weight loss, anorexia, cough, dyspnoea, hepatomegaly, splenomegaly, lymphadenopathy, CNS involvement with confusion or altered mental state
Investigations	- Chest X-ray: Diffuse small nodules ("miliary" pattern) - CT scan: Better visualization of nodules - Blood tests: Anemia, elevated liver enzymes, pancytopenia - TST and IGRA: May assist but can be negative in immunosuppressed patients - Sputum/blood/bone marrow culture: Confirms TB - Lumbar puncture: Rule out tuberculous meningitis
Complications	Respiratory failure, hepatic or renal failure, sepsis, tuberculous meningitis, multi-organ involvement
Management	- **Intensive phase**: 2 months of isoniazid, rifampin, pyrazinamide, ethambutol (HRZE) - **Continuation phase**: 4–7 months of isoniazid and rifampin - **Extended treatment**: Up to 12 months for CNS involvement - **Corticosteroids**: For meningitis or pericarditis



Miliary TB

Non-tuberculous mycobacterial infections

Opportunistic non-tuberculous mycobacteria

- **Mycobacterium avium:** causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm^3.
- **Mycobacterium kansasii:** causes lung disease
- **Mycobacterium malmoense:** most commonly causes pulmonary infection in middle-aged and older adults with pre-existing lung disease or immunodeficiency and can also cause local invasion from a skin lesion.
- **Mycobacterium xenopi** commonly causes lung disease. It has a poor prognosis.
- ***Mycobacterium marinum***: most commonly cause skin infection, produces a **solitary indolent granulomatous lesion - the 'fish tank granuloma',** usually seen in **patients who handle fish** or swim in freshwater or saltwater.

Pathogenesis: colonisation of structurally abnormal lung, for example, in patients with cavitary disease, bronchiectasis, COPD

Diagnosis

- **Cultures: more than two isolates from a non-sterile site are required to establish disease.** (A single isolate can represent contamination.)
- **Chest X-ray:** upper-zone fibrosis and cavitation (like other mycobacterium).

Treatment

- No need to isolate patients or notify public health authorities.
- For lung disease, treatment with azithromycin, rifampin, and ethambutol for 12 months.
- Colonisation of structurally abnormal lung might not always require treatment. However, if treatment is required, then it is usually for longer than the standard 6 months needed to treat pulmonary tuberculosis

Mycobacterium avium causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm3.

The presence of acid fast bacilli (AFB) and absence of TB (Mycobacterium tuberculosis negative on culture.) suggests an atypical AFB such as M. avium.

Atypical mycobacteria differ from M. tuberculosis in that they are ubiquitous organisms (found everywhere) and have no person-to-person spread.

Leprosy

Definition: Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*, an obligate, intracellular, acid-fast bacillus.

Features

- Hypopigmented skin patches, typically affecting the buttocks, face, and extensor surfaces of limbs
- Sensory loss

Types

- The degree of cell-mediated immunity determines the type of leprosy a patient will develop:
  - ⇨ Low degree of cell-mediated immunity → lepromatous leprosy ('multibacillary')
    - extensive skin involvement
    - symmetrical nerve involvement
  - ⇨ High degree of cell-mediated immunity → tuberculoid leprosy ('paucibacillary')
    - limited skin disease
    - asymmetric nerve involvement

Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine
- BNF advice:
  - ⇨ **Multibacillary leprosy (>6 lesions) → rifampicin, dapsone and clofazimine for 12 months.**
  - ⇨ Paucibacillary leprosy (5 or less lesions) → rifampicin and dapsone for 6 months.

Vaccinations

Live attenuated vaccines	
• **BCG** • **Measles, mumps, rubella (MMR)** • **Oral polio** • **Oral rotavirus** • **Oral typhoid**	• **Influenza (intranasal)** • **Yellow fever** • **Varicella** **Live attenuated vaccines are contraindicated in all HIV-positive and immunocompromised patients.**

Inactivated preparations

Whole vaccines	Subunit vaccines (Protein-based)	Subunit vaccines (Polysaccharide-based)
➲ Polio (inactivated vaccine) ➲ Hepatitis A ➲ Rabies ➲ Typhoid ➲ Influenza ➲ Pertussis (cellular vaccine) ➲ Cholera ➲ Japanese encephalitis	➲ Toxoid vaccine ➲ Diphtheria (C. diphtheria) ➲ Tetanus (Clostridium tetani) ➲ Hepatitis B (using the HBsAg) ➲ **Influenza** ➲ Pertussis (acellular vaccine) ➲ HPV ➲ Anthrax	➲ Hib (conjugate vaccine) ➲ Pneumococcal vaccine ➲ PCV13 (conjugate vaccine) ➲ PPSV23 (unconjugated vaccine) ➲ Meningococcal vaccine (conjugate vaccine; various strains of Neisseria meningitidis) ➲ Salmonella typhi

Prophylaxis in splenectomy or asplenia

- **Risk of infection:**
  - Patients with impaired splenic function (eg, splenectomy or asplenic and hyposplenism due to sickle cell disease) are at risk for infection with encapsulated bacteria (eg, Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis)
  - A mnemonic to remember encapsulated bacteria is the **SHiNE SKiS** bacteria (**S**. pneumo, **Hi**b, **N**. meningitidis, **E**. Coli, **S**almonella, **K**lebsiella, Group B **S**trep).

- **Recommended vaccinations**
    - ⇨ S. pneumoniae (pneumococcus): every 5 years
    - ⇨ H. influenzae type b
    - ⇨ N. meningitidis (meningococcus).
    - ⇨ **Annual influenza vaccination** (because influenza is associated with an increased risk of pneumococcal pneumonia)
- **Timing of vaccination for splenectomy:**
    - ⇨ **If elective:** should be completed ≥14 days prior to the procedure
    - ⇨ **If emergency:** should be given 14 days after splenectomy.
- **Daily antibiotic prophylaxis**
    - ⇨ **Indications**:
        - for at least one year following splenectomy.
        - high risk of severe infections (young age, immunocompromised, or history of sepsis caused by encapsulated bacteria).
    - ⇨ **Agents:** daily oral penicillin V or amoxicillin, macrolides is an alternative.

Vaccination for HIV patients

Vaccines that can be used in all HIV-infected adults (inactivated vaccines)	Vaccines that can be used if CD4 > 200	Contraindicated in HIV-infected adults (live vaccines)
• Hepatitis A • Hepatitis B • *Haemophilus influenzae* B (Hib) • Influenza-parenteral • Japanese encephalitis • Meningococcus-MenC • Meningococcus-ACWY I • Pneumococcus-PPV23 • Poliomyelitis-parenteral (IPV) • Rabies • Tetanus-Diphtheria (Td)	• Measles, Mumps, Rubella (MMR) • Varicella • Yellow Fever • shingles vaccine	• Cholera CVD103-HgR • Influenza-intranasal • **Poliomyelitis-oral (OPV)** • Tuberculosis (BCG)

Post-exposure prophylaxis (PEP)

Hepatitis B

- **The risk of HBV transmission if the source has chronic HBV:**
    - ⇨ Vertical transmission (mother to infant): 90%
    - ⇨ Sexual transmission: 18 to 44%
    - ⇨ Percutaneous exposure (e.g., bite or needlestick): 30%
    - ⇨ Breastfeeding does not increase the risk of transmission.
- **How to reduce Mother-to-child transmission?**
    - ⇨ Infant: hepatitis B vaccine and hepatitis B immune globulin [HBIG] within 12 hours of birth.
    - ⇨ Mother: antiviral therapy

	Source person	
Exposed person	**HBsAg positive**	**Unknown**
Responder to HBV vaccine	booster HBV vaccine	booster HBV vaccine
Non-responder	(HBIG) + vaccine	HBIG + vaccine
In the process of vaccination	(HBIG) + vaccine	accelerated course of HBV vaccine (given at zero, one and two months)

Hepatitis C

- PEP not recommended
- Monthly PCR - if seroconversion, then interferon +/- ribavirin

HIV

- **Indications**: Present within 72 hours of exposure
  - ⇨ If the source has HIV
  - ⇨ If the source's HIV status is unknown + the source has risk factors for HIV + high-risk exposure (e.g., unprotected sex) OR the exposed patient has been sexually assaulted
- **Initial management for percutaneous exposure** → wash the area thoroughly
- **When to initiate PEP?** as soon as possible, within 72 hours of the exposure and should not be delayed for HIV testing.
- **Regimen: Three antiretroviral agents for 28 days** ("Truvada®" tenofovir 300mg - emtricitabine 200mg **plus** dolutegravir 50 mg)
- **PEP can be discontinued if testing shows that the source patient is HIV negative.**
- **Testing:**
  - ⇨ Perform HIV antibody testing for at least 6 months post-exposure (e.g., at baselines of 6 weeks, 3 months, and 6 months).
  - ⇨ HIV antigen/antibody tests should not be performed before day 28, since tests for HIV have a "window period" during which time HIV cannot be detected.
  - ⇨ HIV RNA is not routinely used for diagnosis of a new infection
  - ⇨ Test for other bloodborne pathogens (HBV & HCV)
- **Benefit:** Reduces risk of transmission by 80%

Estimates of transmission risk for single needle stick injury

Hepatitis B	**20-30%**
Hepatitis C	0.5-2%
HIV	0.3%

Varicella zoster: VZIG for IgG-negative pregnant women/immunosuppressed

Brucellosis should be suspected in patients with symptoms of (fever, malaise, night sweats, and arthralgia) + animal or animal products exposure (consumption of unpasteurized dairy products)

Brucellosis

Definition: Brucellosis is a zoonotic infection more common in the Middle East and in farmers.

Pathogen: Brucella spp. an intracellular, gram-negative, aerobic, coccobacilli. Four major species cause infection in humans: B melitensis (sheep), B abortus (cattle), B canis and B suis (pigs).

Incubation period 1 - 6 weeks

Transmission: zoonotic

- Contaminated food, esp. raw meat, unpasteurized dairy products
- Contact with infected animals

Pathophysiology: Brucella spp. survive and replicate within macrophages of the reticuloendothelial system → formation of noncaseating granulomas

Features

- Non-specific: fever, (prolonged fever of unknown origin), malaise, night sweats
- Hepatosplenomegaly, painful lymphadenopathy
- Rheumatic features (50%): Arthralgias, low back pain, **spondylitis,** sacroiliitis: (spinal tenderness)
- Osteomyelitis, infective endocarditis, meningoencephalitis, pyelonephritis, epididymo-orchitis.

Diagnosis

- **General:** CBC: may show anemia, neutropenia. LFT: mild elevation of liver enzymes
- **Presumptive diagnosis: Brucella serology** (agglutination test)**:** antibody titer ≥1:160
- **Definitive diagnosis:**
  - ⇨ Culture (from blood, body fluids, or tissue): may be false negative
  - ⇨ Brucella antibody titer: ≥4-fold rise
  - ⇨ Lymph node or bone marrow biopsy → noncaseating granuloma (75% have a positive blood culture and 90% of bone marrow cultures will be positive).

Management

- Combination therapy: **Doxycycline** (100 mg twice daily for 6 weeks a) **PLUS streptomycin** (1g IM once daily for the first 14 to 21 days) or gentamicin (5 mg/kg IV, IM once daily for 7 to 10 days) or doxycycline PLUS rifampin.
- **For pregnant:** (<36 weeks) Rifampin **plus** TMP-SMX. (≥36 weeks): rifampin monotherapy until delivery and continue combination.
- **Focal disease (spondylitis, neurobrucellosis, or endocarditis):** triple-combination for at least 12 weeks and may be up to 6 months.
  - ⇨ **Spondylitis:** doxycycline plus rifampin plus an aminoglycoside (streptomycin or gentamicin)
  - ⇨ **Neurobrucellosis**: ceftriaxone, rifampin, and doxycycline
  - ⇨ **Endocarditis**: aminoglycoside (streptomycin or gentamicin) for the first month, PLUS rifampin and doxycycline for at least 12 weeks and may be up to 6 months.

Cat scratch disease (CSD)

Definition: a benign, self-limiting infectious disease that is transmitted mainly by cats (via scratching, biting, or licking)

Pathogen: Gram negative rod *Bartonella henselae*

Features

- fever, headache, malaise
- history of a cat scratch
- **regional lymphadenopathy**
- **In immunocompromised individuals** (e.g., patients with HIV) → **Bacillary angiomatosis** (vascular proliferation, which leads to the development of solitary or multiple, red-purple papules that bleed easily).

Treatment

- Mild or moderate cases: azithromycin (5-day course) to decrease lymphadenopathy and the duration of illness
- In the case of persistent and/or disseminated disease (e.g., bacillary angiomatosis): erythromycin OR doxycycline
- In the case of CNS involvement or endocarditis: rifampicin PLUS either erythromycin OR doxycycline

Whooping cough (pertussis)

Bacteria

- Caused by the bacterium *Bordetella pertussis*, a gram-negative aerobic coccobacillus
- The virulence factors of Bordetella pertussis include its eponymous toxin and tracheal cytotoxin,

Epidemiology: now more common in adolescents and adults than in children.

Mechanism: the **tracheal cytotoxin** from Bordetella pertussis kills ciliated cells along the respiratory epithelium.

Features: pertussis has three major phases:

- Catarrhal phase (like the common cold)
- Paroxysmal phase (bouts of coughing)
- Convalescent phase (resolution).
- Lymphocytosis is typically found.

Complications

- Pneumonia, seizures, and encephalopathy
- **Hemiseizure-hemiplegia syndrome, a rare complication** which is thought to be related to post-immunisation hyperthermia rather than direct neurological toxicity.

Treatment: supportive + antibiotics (erythromycin, clarithromycin and azithromycin are first choice)

Prevention: diphtheria-pertussis-tetanus (DPT) vaccine (63% to 94% effective)

Cholera

Pathogen

- Caused by Vibro cholerae - Gram-negative bacteria
- Because the organism is not acid-resistant, it **depends on its large inoculum size** (infectious dose) to **withstand gastric acidity.**
  - ⇨ If ingested with water, a higher infectious dose is needed. When ingested with food, fewer organisms are required to produce disease.
  - ⇨ ↓ Gastric acidity (anti-acid drugs, gastrectomy) → ↑risk of cholera infection and severity

Mechanism by which cholera leads to fluid loss:

- Cholera toxin has two parts, A and B.
  - ⇨ B subunits bind to a ganglioside (monosialosyl ganglioside, **GM1 receptor**) located on the surface of the cells that line the intestinal mucosa.
  - ⇨ B binds while A activates **G protein → activates adenylate cyclase → ↑(cAMP)** → unrestricted chloride secretion from villous **crypts.**

Features

- Profuse 'rice water' diarrhoea
- Dehydration
- Hypoglycaemia:, hypoglycemia is the most common lethal complication of cholera in children after dehydration.

Management

- Oral rehydration therapy
- Antibiotics: doxycycline, ciprofloxacin

Chickenpox (Varicella-zoster virus)

Definition:

- Chickenpox is an acute, highly contagious viral infection caused by the varicella-zoster virus (VZV), which is part of the herpesvirus family. It is characterised by fever and a vesicular rash. The virus can remain dormant and reactivate later in life, leading to herpes zoster (shingles).
- Shingles is reactivation of dormant virus in dorsal root ganglion

Epidemiology:

- Primarily affects children, with a peak incidence between 1-9 years.
- Highly contagious, with 80-90% secondary attack rates in susceptible individuals.
- Adults and immunocompromised patients are at higher risk for complications.
- It s commonest in spring time.

Transmission:

- **Spread through** direct contact with fluid from vesicles or respiratory droplets from coughing/sneezing.
- **Contagious** from 1-2 days before the rash until all lesions have crusted over. **Transmission has never been reported beyond the fifth day of the rash.'**
- **Incubation period:** 10-21 days.

Clinical Features:

- **Prodrome** (common in adults, less so in children): Mild fever, malaise, headache.
- **Rash**:
  - ⇨ Starts as macules, progressing to papules, vesicles, pustules, and finally crusted lesions.
  - ⇨ Appears first on the face and trunk, spreading to limbs.
  - ⇨ "Crops" of new lesions appear over 2-4 days.
- **Fever**: Generally mild in children; higher and more prolonged in adults.

Complications:

- **Common Complications**:
  - ⇨ **Bacterial superinfection**: Impetigo and cellulitis.
  - ⇨ **Dehydration**: Due to poor oral intake and high fever.
- **Serious Complications**:
  - ⇨ **Pneumonia**: Especially in adults, pregnant women, and immunocompromised individuals.
  - ⇨ **Encephalitis**: Rare but serious, presenting with altered consciousness and seizures.
  - ⇨ **Hepatitis**: Typically in immunocompromised or pregnant women.
- **Reactivation**: **Herpes zoster (Shingles)**: Reactivating dormant VZV in dorsal root ganglia leads to dermatomal pain and vesicular rash.

Risk Groups for Severe Disease:

- **Immunocompromised patients** (e.g., **HIV**, chemotherapy, steroids).
- **Pregnant women** (especially 13-20 weeks gestation).
- **Neonates** (especially if maternal infection occurs close to delivery).
- **Adults** (particularly those >20 years old).

Diagnosis:

- **Clinical Diagnosis**: Characteristic rash is typically sufficient for diagnosis.
- **Laboratory Tests** (when necessary):
  - ⇨ **PCR** from vesicular fluid (gold standard).
  - ⇨ **Serology**: Detecting IgM antibodies in primary infection.
  - ⇨ **Tzanck smear**: Can show multinucleated giant cells (less commonly used).

Management:

- **General Supportive Care**:
  - ⇨ Antipyretics (avoid aspirin due to the risk of Reye's syndrome).
  - ⇨ Antihistamines to reduce pruritus. calamine lotion
  - ⇨ Adequate hydration.
- **Antiviral Treatment**:
  - ⇨ **Acyclovir**: Indicated for:
    - Adults (>14 years old) within 24 hours of rash onset. Because it can lessen the occurrence of post-herpetic neuralgia.
    - Immunocompromised patients.
    - Pregnant women with chickenpox (especially if at risk of complications).
  - ⇨ Aciclovir (also famciclovir, and ganciclovir) acts through inhibition of viral (DNA) polymerase but it is a pro-drug and first requires phosphorylation by thymidine kinase. Resistance arises when the virus lacks thymidine kinase.

- ⇨ Cidofovir does not require activation by viral thymidine kinase; therefore, it would be best suited to treat the thymidine kinase-deficient varicella-zoster virus.
- ⇨ **Intravenous acyclovir** for severe cases or complications (e.g., pneumonia, encephalitis).
- **Varicella-Zoster Immunoglobulin (VZIG)**:
  - ⇨ Post-exposure prophylaxis should be initiated within 10 days of exposure in high-risk groups (e.g., immunocompromised and pregnant women).
- **Isolation**: Until all lesions are crusted to prevent transmission, particularly in hospitals.

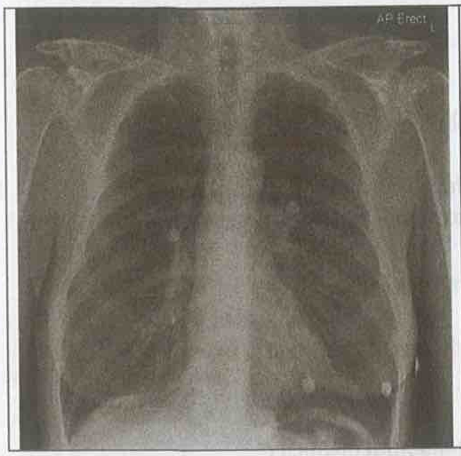
Vaccination:

- **Varicella Vaccine**:
  - ⇨ Live attenuated vaccine given as part of the childhood immunisation schedule in many countries.
  - ⇨ **Post-exposure prophylaxis:** Can be administered within 72 hours of exposure to prevent or mitigate the disease.
- **Zoster Vaccine**:
  - ⇨ Recommended for adults >50 years to prevent herpes zoster (shingles) and its complications (e.g., postherpetic neuralgia).

Pregnancy and Chickenpox:

- **Maternal Risk**:
  - ⇨ Pregnant women are at higher risk for severe disease, including pneumonia and hepatitis.
- **Fetal Risks**:
  - ⇨ **Congenital Varicella Syndrome (CVS)**: Associated with infection in the first 20 weeks of gestation, causing **limb hypoplasia**, scarring, and microcephaly.
  - ⇨ **Neonatal Varicella**: Occurs if maternal infection occurs 5 days before or 2 days after delivery, leading to severe neonatal infection.
- **Management in Pregnancy**:
  - ⇨ **Acyclovir** for pregnant women with severe disease.
  - ⇨ **VZIG** for susceptible pregnant women post-exposure.

- **Risks of complication to the mother:** 5 times greater risk of pneumonitis
- **Management of chickenpox exposure:** **Check for varicella antibodies**
  - ⇨ If not immune to varicella → give varicella zoster immunoglobulin (**VZIG is effective up to 10 days post-exposure**)
  - ⇨ If present within 24 hours of the rash → give oral acyclovir
- **Varicella zoster immunoglobulin** (VZIG): VZIG prophylaxis is recommended for patients who fulfil all the following criteria:
  1. Risk of severe varicella (for example, immunosuppression, neonates, **pregnant women**)
  2. No antibodies to varicella zoster
  3. Significant exposure to chickenpox or herpes.



Chest X-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities are noted throughout both lungs. These are uniform in size and dense, suggesting calcification. No focal lung parenchymal mass or cavitating lesion was seen. The appearances are characteristic of healed varicella pneumonia.

Chickenpox exposure in pregnancy - the first step is to check antibodies.

Cytomegalovirus

Definition

- Cytomegalovirus (CMV) is a **herpesvirus** that can cause asymptomatic infection or disease ranging from mild illness to severe, life-threatening complications, particularly in immunocompromised patients.

Transmission

- Spread through direct contact with body fluids: **saliva, urine, blood, sexual fluids, and breast milk.**
- **Vertical transmission**: Mother-to-fetus via the placenta (congenital CMV).
- **Blood transfusion or organ transplantation** can also spread CMV.

Pathophysiology

- After primary infection, CMV establishes **lifelong latency** within monocytes and bone marrow cells, reactivating under conditions of immunosuppression.

Clinical Features

- **Healthy individuals:** Often asymptomatic or mild flu-like illness.
- **Immunocompromised patients (e.g., transplant recipients, HIV):**
  - CMV pneumonitis
  - CMV retinitis (blurred vision or vision loss)
  - CMV colitis (diarrhea, abdominal pain)
  - CMV encephalitis or hepatitis.
- **Congenital CMV:**
  - Hearing loss, developmental delays, microcephaly, and vision problems in infants.

Diagnosis

- **Serology (IgM/IgG):** Detects recent or past infection.
- **PCR:** Detects viral DNA in blood or tissue.
- **Histology:** Inclusion bodies (called "owl's eye" appearance) in infected tissues.
- **Culture:** Virus isolation from blood or tissue.
- **Screening for congenital CMV:** CMV detection in urine or saliva within 3 weeks of birth.

Treatment
- **First-line treatment:**
  - *Ganciclovir* (IV) or *Valganciclovir* (oral).
  - **Dose of valganciclovir:** 900 mg twice daily for 21 days, followed by maintenance dosing (900 mg once daily).
- **Second-line treatment:** *Foscarnet* or *Cidofovir* (for ganciclovir-resistant cases).
- **Supportive care:** Particularly for complications like CMV colitis or encephalitis.

Prevention
- **Prophylaxis:** Valganciclovir in high-risk transplant recipients.
- **Preemptive monitoring:** Routine CMV viral load testing post-transplant.
- **Prevention in pregnancy:** CMV screening in early pregnancy; avoid exposure to CMV-infected individuals.

Complications
- **Congenital CMV:** Hearing loss, microcephaly, intellectual disability.
- **Immunocompromised patients:** CMV pneumonitis, retinitis, colitis, or systemic infections leading to organ damage and death.

Dengue fever
Pathogen
- **Caused by** Dengue virus , RNA virus of the genus Flavivirus
- **Transmitted** by the Aedes aegyti mosquito
- **Incubation period 4-10 days.**
- **Distribution:** tropical regions worldwide, particularly Asia (e.g., Thailand)
- Most common viral disease affecting tourists in tropical regions

Features
- Headache (often retro-orbital)
- Fever, scleral injection
- Myalgia (severe musculoskeletal pain is a prominent feature) hence the name breakbone fever.
- Pleuritic pain
- Facial flushing (dengue)
- Maculopapular rash may develop in recovery phase
- Epistaxis and scattered petechiae may be observed.

Complication
- **Dengue haemorrhagic fever (DHF):** a form of disseminated intravascular coagulation (DIC) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

Laboratory tests
- CBC: Leukopenia, Neutropenia, Thrombocytopenia
- ↑ AST

Diagnosis: dengue fever serology.

Treatment: symptomatic e.g. fluid resuscitation, blood transfusion etc

Yellow fever

Definition

- Yellow fever is a viral hemorrhagic disease caused by the *Yellow fever virus*, a flavivirus transmitted by mosquitoes (*Aedes aegypti*). It mainly occurs in tropical regions of Africa and South America.

Transmission and Epidemiology

- **Transmission:** Spread by mosquito bites, primarily in jungle and urban areas.
- **Geography:** Endemic to Africa and South America.
- **Reservoirs:** Monkeys are a natural reservoir in jungle cycles, while humans are the main host in urban outbreaks.

Clinical Features

1. **Incubation period:** 3-6 days
2. **Phases:**
   - **Initial Phase (acute phase):**
     - Fever, headache, muscle pain, backache
     - Nausea, vomiting, dizziness
   - **Toxic Phase (severe disease):**
     - Jaundice, bleeding (e.g., nose, mouth, eyes, stomach)
     - Kidney failure and liver dysfunction
     - High fever, organ failure, shock, and death in severe cases.

Diagnosis

- **Clinical history and symptoms:** Recent travel to endemic areas.
- **Laboratory tests:**
  - ELISA or PCR for yellow fever RNA.
  - Liver function tests (elevated bilirubin, ALT/AST).
  - Blood smear to exclude malaria.

Complications

- **Severe complications:** Hepatic failure, renal failure, hemorrhagic manifestations.
- **Mortality:** Case-fatality rate is 20-50% among severe cases.

Prevention

1. **Vaccination:**
   - Single-dose *live-attenuated vaccine* (effective for life).
   - Recommended for people traveling to or living in endemic areas.
2. **Mosquito Control:** Use of insect repellent, wearing protective clothing, and sleeping under mosquito nets.

Treatment

- **Supportive care:** There is no specific antiviral treatment

Yellow fever is suggested by:
1. **Travel to endemic area (West Africa and Central America)**
2. **Fever, with initial resolution**
3. **Progression to jaundice and renal failure**

Sexually Transmitted Infections (STI)

Human immunodeficiency virus (HIV)

Definition

- HIV is a retrovirus that primarily targets the immune system, specifically CD4+ T lymphocytes, leading to immunodeficiency.
- If untreated, it can progress to acquired immunodeficiency syndrome (AIDS), characterised by life-threatening infections and cancers due to immune suppression.

Pathophysiology

- HIV infects CD4+ T-cells, macrophages, and dendritic cells by binding to the CD4 receptor and coreceptors (CCR5 or CXCR4).
- The virus integrates into the host genome, leading to chronic infection. Over time, this depletes CD4+ T-cell counts, resulting in immunosuppression.
- Without treatment, chronic immune activation and viral replication cause progressive immune decline.

Routes of transmission

- Sexual: responsible for ~ 80% of infections worldwide
- Parenteral transmission
- Needle sharing: → 0.67%
- Vertical transmission: from mother to child during childbirth (~ 5–15%)

Clinical Features

- **Acute HIV infection:** Flu-like symptoms (fever, sore throat, rash, lymphadenopathy).
- **Chronic HIV infection:** Often asymptomatic for years; mild infections like oral candidiasis or herpes zoster may occur.
- **AIDS:** Opportunistic infections (e.g., Pneumocystis pneumonia) or malignancies (Kaposi's sarcoma, lymphoma).

Associated Conditions

- **Opportunistic Infections:**
  - Pneumocystis jirovecii pneumonia (PCP), Tuberculosis (TB), Cytomegalovirus (CMV), Toxoplasmosis. **Unlike oral candidiasis, oesophagal candidiasis is an AIDS-defining condition.**
- **Malignancies:**
  - Kaposi's sarcoma, Non-Hodgkin's lymphoma, Cervical cancer.
- **Neurocognitive Disorders:**
  - HIV-associated neurocognitive disorder (HAND).
- **HIV nephropathy**
  - Normal-sized kidneys on ultrasound scan
  - **Focal segmental glomerulosclerosis on renal biopsy**
  - Normotension

Step-by-Step Diagnostic Approach

1. **Initial Screening Test:**
    - Fourth-generation HIV antigen/antibody combination assay (detects both p24 antigen and antibodies).
2. **Confirmatory Testing:**
    - If the screening is positive, follow with an HIV-1/HIV-2 differentiation immunoassay.
3. **HIV RNA PCR:**
    - Used in cases of acute infection when antibody response is not yet detected.
4. **CD4 Count & Viral Load:**
    - Monitors disease progression and response to treatment.
5. **Drug Resistance Testing:**
    - Assesses viral mutations for resistance to antiretroviral drugs.

Treatment

- **start ART in every HIV-positive individual, regardless of CD4 count.**
    - Standard ART: A combination of at least three antiretroviral drugs from two different classes.
        - NRTIs (Nucleoside Reverse Transcriptase Inhibitors): Tenofovir, Lamivudine
        - NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors): Efavirenz
        - PIs (Protease Inhibitors): Atazanavir
        - INSTIs (Integrase Inhibitors): Dolutegravir, Bictegravir
        - CCR5 Antagonists: Maraviroc
    - Treatment Regimen Example: Dolutegravir + Tenofovir/Emtricitabine (TDF/FTC)
- **In hepatitis B co-infection**
    - ⇨ **Antiretrovirals that also have anti-HBV activity should be included in the regimen used to treat HIV.** These include Emtricitabine, Lamivudine and Tenofovir.
    - ⇨ Discontinuation of drugs that have anti-HBV activity can lead to reactivation of HBV and cause serious hepatocellular damage.
- In patients with renal impairment → avoid **tenofovir** and consider avoiding atazanavir.
- **Efavirenz is the only antiretroviral medication that is contraindicated in pregnancy (teratogenic)**

Treatment Complications

- **Short-term:** Headache, nausea, diarrhoea
- **Long-term:**
    - **Metabolic syndrome** (e.g., insulin resistance, dyslipidemia)
    - **Bone demineralization** (osteopenia/osteoporosis with tenofovir)
    - **Neuropsychiatric symptoms** (e.g., insomnia with efavirenz)
    - **Renal toxicity** (e.g., tenofovir-induced nephropathy)

Unlike oral candidiasis, esophageal candidiasis is an AIDS-defining condition.

Anti-retroviral therapy (ART) in HIV

Drug Class	Examples	Side Effects
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	(ine at the end) ▪ Zidovudine (AZT) ▪ Lamivudine ▪ Stavudine ▪ Didanosine ▪ Emtricitabine ▪ Abacavir(the only NARTI which is not ended by (ine)	- Mitochondrial toxicity: Peripheral neuropathy, dilated cardiomyopathy, pancreatitis, lactic acidosis - **Zidovudine:** Anaemia (marrow suppression), macrocytosis, myopathy, black nails - **Abacavir:** Hypersensitivity in HLA-B5701 positive patients - **Emtricitabine:** Hyperpigmentation of palms in 8% of black patients
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	(vir in the middle) ▪ Nevirapine ▪ Delavirdine ▪ Efavirenz ▪ Etravirine	- **Nevirapine:** P450 induction, acute hepatitis, hypersensitivity skin rash - **Efavirenz:** Neuropsychiatric side effects, gynecomastia - General: Skin rashes
Protease Inhibitors (PI)	(vir at the end) ▪ Indinavir ▪ Nelfinavir ▪ Ritonavir ▪ Saquinavir	- Metabolic: Diabetes, hyperlipidemia, hypertriglyceridemia, buffalo hump, central obesity, lipodystrophy (loss of adipose tissue) - **Indinavir:** Renal stones, asymptomatic hyperbilirubinemia - General: P450 inhibition

Preventing Opportunistic Infections in Patients With HIV

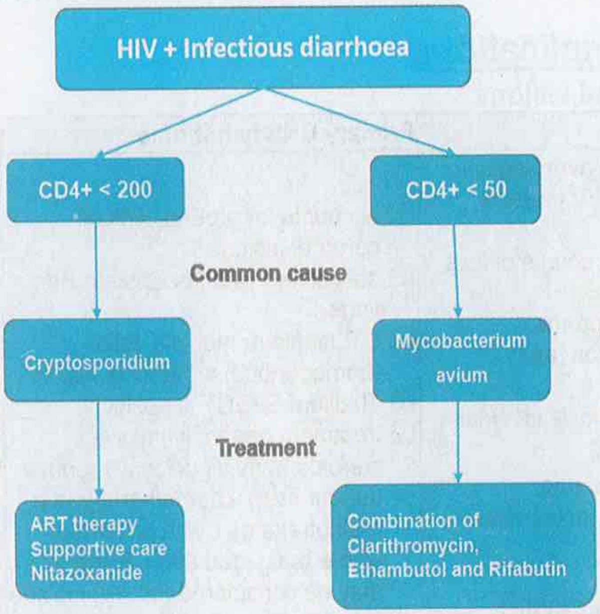
Co-trimoxazole prophylaxis for *Pneumocystis* (PCP) is not necessary unless the CD4 count is below 200

- **CD4 counts are useful landmarks for initiation of antimicrobial prophylaxis:**
  - ⇨ **Less than 250 cells/μL → Coccidioidomycosis** prophylaxis if seropositive in high-risk area→ fluconazole 400 mg PO daily. continue until the CD4 count exceeds 250 cells/μL for 6 month.
  - ⇨ **Less than 200 cells/μL → PCP prophylaxis** → trimethoprim-sulfamethoxazole 1 double-strength tablet orally daily or 1 double-strength tablet orally 3 times weekly. continue until the CD4 count exceeds 200 cells/μL **for 3 months.**
  - ⇨ **Less than 150 cells/μL → Histoplasmosis** prophylaxis if high-risk exposure (hyperendemic area)→ itraconazole 200 mg PO daily. continue until the CD4 count exceeds 150 cells/μL for 6 months.
  - ⇨ **Less than 100 cells/μL → Toxoplasmosis** prophylaxis (if seropositive) →Trimethoprim-sulfamethoxazole, one double-strength tablet orally once daily is preferred
  - ⇨ **Less than 50 cells/μL → Mycobacterium avium complex** prophylaxis → azithromycin 1200 mg orally **weekly** (preferred) or clarithromycin 500 mg orally twice daily or rifabutin 300 mg orally daily

Immune reconstitution inflammatory syndrome (IRIS) (also known as **immune recovery syndrome**)

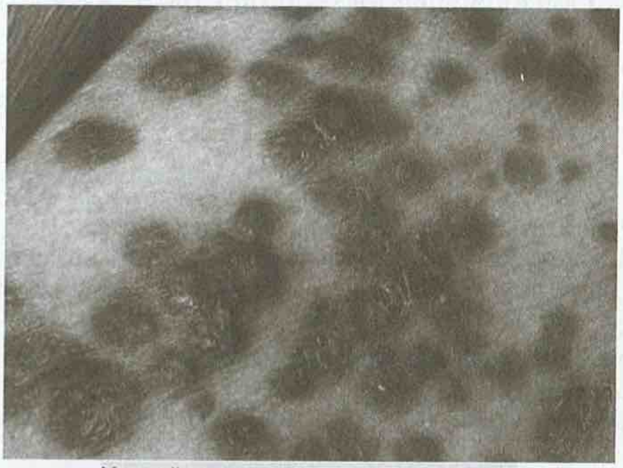
- **Definition:** an inflammatory syndrome that can occur **after initiation of ART** and consists of either the appearance of a new condition or worsening of a preexisting condition
- **Occurs in ~ 15–25% of patients starting ART**
- **Mechanism:** Starting **ART** in AIDS → the immune system begins to recover → responds to a previously acquired opportunistic infection (eg, mycobacteria, HSV, CMV, Cryptococcus) with an overwhelming inflammatory response → paradoxically makes the symptoms of infection worse (clinical deterioration and localized tissue inflammation)
- **Risk factors:** Low CD4 count (especially CD4 < 50)
- **Occurs typically 4-8 weeks after starting treatment**
- **Often presents with enlarging lymph nodes**
- **Treatment:** self-limited. Do not interrupt ART + add steroids for severe cases

HIV-associated diarrhoea



HIV-associated Kaposi sarcoma

- **Definition:** a **neoplasm of endothelial cells** (vascular tumour) **caused by human herpes virus 8 (HHV-8),** most commonly seen in patients with HIV and transplant patients.
- **Feature: purple papules or plaques** on the skin or **mucosa** (e.g. gastrointestinal and respiratory tract), commonly on the face
- **Diagnosis:** Histopathology: **lymphocytic inflammation** & proliferation of endothelial cells (**spindle cells**)
- **Treatment:** 1st line → Highly active antiretroviral therapy (HAART). Other measures → radiotherapy, chemotherapy


Kaposi's sarcoma in a patient with HIV

HIV neurocomplications

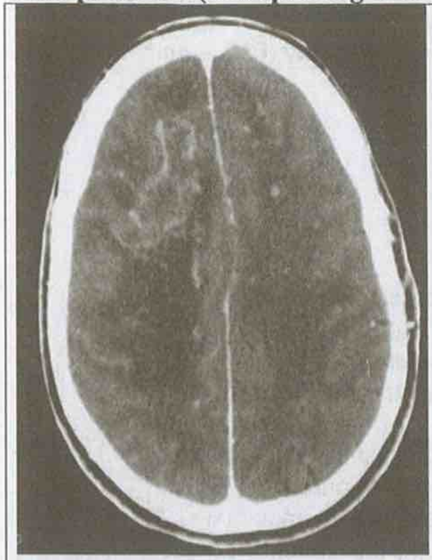
Focal neurological lesions

Toxoplasmosis	Primary CNS lymphoma	Tuberculosis
🕮 the most common neurological infection seen in HIV patients (50%) 🕮 Occurring at CD4 counts of less than 100 cells/mm3. 🕮 constitutional symptoms, headache, confusion, and drowsiness 🕮 Positive toxoplasmosis IgG in the serum 🕮 CT or MRI: multiple ring enhancing lesions, mass effect may be seen 🕮 Thallium SPECT is negative 🕮 management: sulfadiazine and pyrimethamine	🕮 accounts for around 30% of cerebral lesions 🕮 associated with the Epstein-Barr virus 🕮 CT: single or multiple solid (homogenous) enhancing lesion 🕮 Thallium SPECT is positive 🕮 treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours	🕮 much less common than toxoplasmosis or primary CNS lymphoma 🕮 CT: single enhancing lesion

Differential diagnosis of ring-enhancing lesions on CT in a patient with AIDS:

- Cerebral toxoplasmosis (most common)
- Atypical CNS lymphoma
- Abscesses
- Metastases

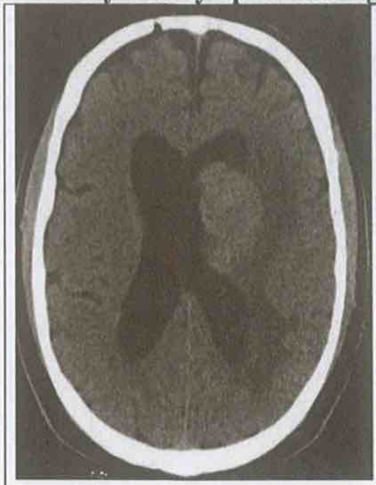
Toxoplasmosis (multiple ring-enhancing lesions)



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions

Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

Primary CNS lymphoma: single or multiple solid (homogenous) enhancing lesions:



Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.

Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Generalised neurological disease

Encephalitis	Cryptococcus	Progressive multifocal leukoencephalopathy (PML)	AIDS dementia complex
🕮 may be due to CMV or HIV itself 🕮 HSV encephalit is is relatively rare in the context of HIV 🕮 CT: oedemato us brain	🕮 most common fungal infection of CNS 🕮 headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit 🕮 associated with raised intracranial pressure →papilledema and the falsely localizing 6th nerve palsy. 🕮 CSF: high opening pressure, India link test positive 🕮 CT: meningeal enhancement, cerebral oedema 🕮 meningitis is typical presentation but may occasionally cause a space occupying lesion 🕮 Management: IV anti-fungal, such as amphotericin B and flucytosine. Therapeutic lumber puncture → reduce ICP. Anti-retroviral therapy (ART) should be delayed for few weeks, (due to ↑risk of developing IRIS (immune reconstitution inflammatory syndrome) if ART started immediately).	🕮 widespread demyelination 🕮 due to infection of oligodendrocytes by JC virus (a polyoma DNA virus) 🕮 symptoms, subacute onset : behavioural changes, speech, motor, and visual impairment 🕮 CT: single or multiple lesions, no mass effect, do not usually enhance. MRI is better; high-signal demyelinating white matter lesions are seen	🕮 caused by HIV virus itself 🕮 symptoms: behavioural changes, motor impairment 🕮 CT: cortical and subcortical atrophy

CT findings of HIV neuro-complications

Condition	CT finding
Toxoplasmosis	**Multiple** lesions Ring or nodular enhancement **Thallium SPECT negative**
Lymphoma	**Single** lesion Solid (homogenous) enhancement **Thallium SPECT positive**
Tuberculosis	Single enhancing lesion
Encephalitis	Oedematous brain
Cryptococcus	Meningeal enhancement, cerebral oedema
Progressive multifocal leukoencephalopathy (PML)	Single or multiple lesions **No mass effect** **Don't usually enhance**
AIDS dementia complex	Cortical and subcortical atrophy

Vaginal discharge

Causes: Vaginal discharge is a common presenting symptom and is not always pathological.

Common causes	Less common causes
• Physiological • *Candida* • *Trichomonas vaginalis* • Bacterial vaginosis	• *Gonorrhoea* • *Chlamydia* can cause a vaginal discharge although this is rarely the presenting symptoms • ectropion • foreign body • cervical cancer

Key features of the common causes of vaginal discharge

Condition	Key notes
Candida	• **Cottage cheese** discharge, Vulvitis, Itching • Treatment: 150 mg single dose of oral fluconazole.

Condition	Key notes
Trichomonas vaginalis	• Anaerobic flagellated protozoan • Offensive, **yellow/green**, frothy discharge • Vulvovaginitis, vulvar pruritus • **Strawberry cervix** • ↑ vaginal pH > 4.5 • Diagnosis: **wet mount** demonstrates **motile flagellated protozoans**. • **Treatment: single-dose (2g) tinidazole or metronidazole (metronidazole preferred in pregnancy) + screened for other STDs** • **Abstain from sex until treated + partner screening (breastfeeding should be stopped during metronidazole course)**
Bacterial vaginosis	• **Not sexually transmitted but found exclusively in sexually active women.** • **The commonest cause of abnormal vaginal discharge** in women of childbearing age. • Key features: Offensive, thin, **white/grey**, 'fishy odor' discharge • **No soreness or irritation (unlike *Trichomonas vaginalis*)** • ↑ vaginal pH > 4.5 • Predominant organism: **Gardnerella vaginalis** • **Microscopic finding: Epithelial cells with a stippled border (Clue cells)** • **Treatment: oral metronidazole (can be used throughout pregnancy)**

Genital ulcers (STI)

Genital ulcers:

- **Painful**: herpes much more common than chancroid
- **Painless**: syphilis more common than lymphogranuloma venereum + granuloma inguinale

Genital ulcers caused by STIs

Cause	Key notes
Genital herpes	➲ **Most common** painful genital ulcer (commoner than chancroid) ➲ **Caused** by herpes simplex type 2 (type 1 commonly cause oral ulcer). ➲ **Feature: Multiple painful penile vesicles and ulcers** ➲ **Diagnostic test:** PCR ➲ **Treatment:** Oral Acyclovir ➲ **Prognosis:** heal within 2 weeks. Recurrent
Chancroid	➲ **Caused by** *Haemophilus ducreyi.* ➲ Painful genital ulcers, sharply defined, ragged, undermined border, bleeds on contact. Unilateral, painful inguinal lymph node enlargement. ➲ **Diagnosis:** isolation of *H ducreyi* on special media. PCR → rapid detection of *H ducreyi.* ➲ **Treatment:** single dose oral azithromycin or IM ceftriaxone + treat sexual partner + screen for the other STDs (syphilis, HSV, gonorrhea, chlamydia and HIV).
Lymphogranuloma venereum	➲ **Caused by** *Chlamydia trachomatis* ➲ **Stage 1:** painless pustule →ulcer (3-12 days later) ➲ **Stage 2:** painful inguinal lymphadenopathy (1-6 months later) → thin overlying skin → abscesses. Groove sign (separation inguinal nodes by the inguinal ligament) → characteristic. ➲ **Stage 3:** proctocolitis (tenesmus, strictures and fistulas). Cervicitis & urethritis. ➲ **Diagnosis:** serology tests (complement fixation or micro-immunofluorescence) or identification of Chlamydia trachomatis in genital, rectal and lymph node specimens (by culture, nucleic acid amplification test or direct immunofluorescence). ➲ **Treatment:** doxycycline 100 mg orally twice daily or erythromycin 500 mg orally four times a day for 21 days.
Syphilis	➲ **Caused by** the spirochaete Treponema pallidum. ➲ **Chancre** (painless ulcer at the site of sexual contact + local non-tender lymphadenopathy). Primary syphilis occurs 14 days to 3 months post exposure. ➲ **Diagnosis:** VDRL/RPR (a rapid but nonspecific screening test), and/or a FTA-ABS (specific and diagnostic, the gold standard) ➲ **Treatment:** single doses of benzathine penicillin 2.4 million IM) (First-line) OR doxycycline OR erythromycin (if allergic to penicillin).
Granuloma inguinale (Donovanosis)	➲ **Caused by** Klebsiella granulomatis ➲ **Feature:** non-tender, beefy-red ulcerative lesion that bleeds easily. ➲ **Diagnosis:** biopsy → donovan bodies ➲ **First-line treatment** is azithromycin 1 g followed by 500 mg daily, until all lesions are healed.

Cause	Key notes
Venereal warts (genital warts) (condylomata acuminata)	➲ **Caused by** human papillomavirus (HPV) ➲ **Feature:** Painless, soft, fleshy, slightly pigmented "cauliflower like lesion" on the vulva, vaginal wall, cervix, or perineum, may bleed or itch. ➲ **HPV →↑ risk of cancer** (**most commonly HPV 16** → squamous cell carcinomas in cervix, anus and penis.) ➲ **Diagnosis:** biopsy to detect condylomata acuminata ➲ **Treatment:** topical podophyllum or cryotherapy (the majority cleared without intervention within 1-2 years, and recurrence is common) ▪ 1st line: topical podophyllum or cryotherapy 🕮 Multiple, non-keratinised warts → topical podophyllum 🕮 solitary, keratinised warts → cryotherapy ▪ 2nd line: **topical imiquimod**

Herpes simplex virus

Pathogen

- Herpes simplex virus is a DNA virus.
- There are two strains of the herpes simplex virus (HSV) in humans:
  1. **HSV-1 → most commonly cause orofacial disease**
  2. **HSV-2 → most commonly cause genital disease**.
- **Incubation period** → 2 days to 2 weeks.

Transmission: Direct contact with mucosal tissue or secretions of another infected person (HSV-1 via saliva and HSV-2 through genital contact.)

Pathophysiology

- **Inoculation:** The virus enters the body through mucosal surfaces or small dermal lesions.
- **Neurovirulence:** The virus invades, spreads, and replicates in nerve cells.
- **Latency:** After primary infection, the virus remains dormant in the ganglion neurons.
  - ⇨ Trigeminal ganglion: HSV-1
  - ⇨ Sacral ganglion: HSV-2
- **Reactivation:** triggered by various factors (e.g., immunodeficiency, stress, trauma)

Features

- Up to **80%** of herpes simplex infections are **asymptomatic**.
- **Gingivostomatitis and pharyngitis** are the most common manifestations of primary HSV-1 infection, whereas **herpes labialis** (vesicles that turn into painful ulcers in oral mucosa and lip borders) is the most frequent sign of reactivation disease.
- **Genital herpes (herpes genitalis):** HSV-2, but HSV-1 also can cause → **painful genital ulceration +** painful bilateral lymphadenopathy in the groin area.
- **Herpetic whitlow: grouped, non-purulent vesicles on an erythematous base,** may rupture or ulcerate, involved one or more fingers (**especially the thumb and index fingers**); mostly found on terminal phalanx and associated with axillary and epitrochlear **lymphadenopathy.**

Diagnosis

- **Mucocutaneous HSV infections are primarily a clinical diagnosis** based on the classic appearance of vesicular and ulcerative lesions
- **Confirmatory testing:**
  - ⇨ **PCR:** **Nucleic acid amplification test (NAAT)** → detect HSV DNA from a genital ulcer or mucocutaneous lesion sample (**most sensitive, 1st line test for confirmation**)
  - ⇨ Microscopic: **Tzanck test** → Multinucleated giant cells + Eosinophilic intranuclear Cowdry A inclusions (**not recommended due to poor sensitivity and specificity.**)

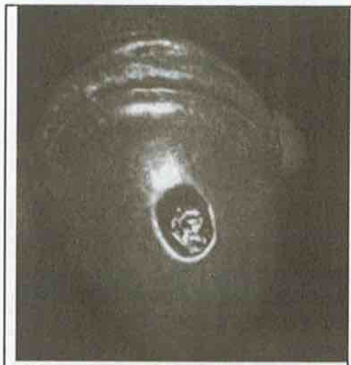
Management

- **Mucocutaneous herpes (e.g., gingivostomatitis or pharyngitis) and genital herpes:** oral acyclovir (eg, 400 mg three times daily), famciclovir (500 mg twice daily), or valacyclovir (1 g twice daily) for 7 to 10 days. Valacyclovir is preferred. No role for topical therapy.

Syphilis

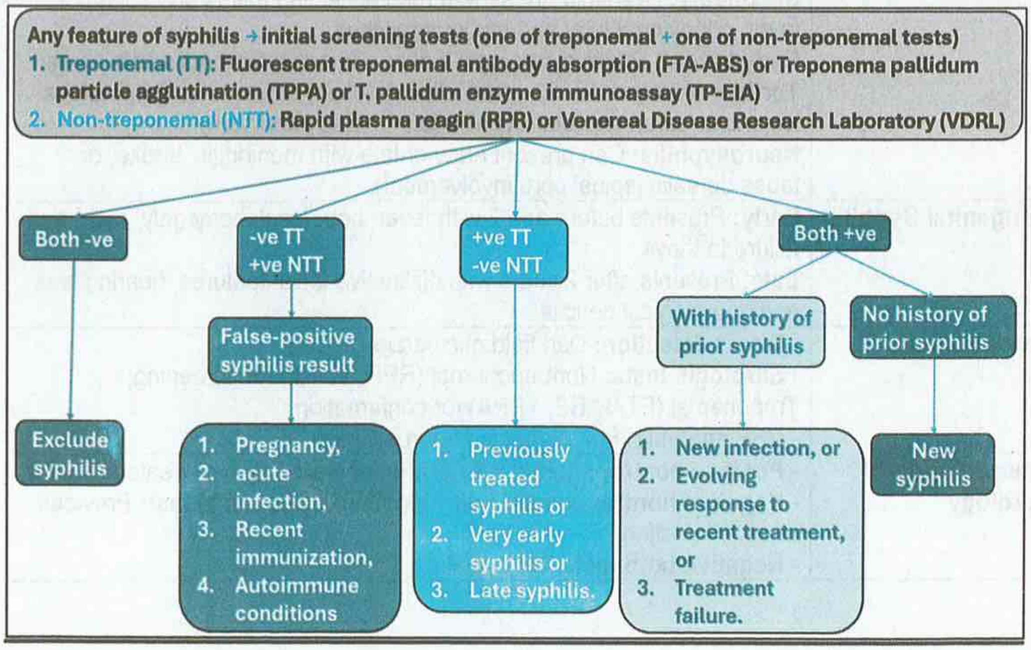
Aspect	Details
Definition	A sexually transmitted infection caused by *Treponema pallidum*, a spirochete bacterium. Incubation: 9–90 days.
Risk of Infection	1/3 of sexual contacts with infected individuals develop syphilis.
Types of Syphilis	**Primary:** Single painless chancre with regional adenopathy; heals in 3–6 weeks. **Secondary:** Systemic illness with rash (including palms and soles), fever, condyloma lata, and mucous patches. **Early Latent:** Positive serologic testing without symptoms within 1 year. **Tertiary:** Appears 15–30 years after infection; presents as gummatous lesions or cardiovascular syphilis (e.g., aortic aneurysm). **Neurosyphilis:** Can present early or late with meningitis, stroke, or tabes dorsalis (spinal cord involvement).
Congenital Syphilis	**Early:** Presents before age 2 with fever, hepatosplenomegaly, rash, and failure to thrive. **Late:** Presents after 2 years with distinctive facial features, hearing loss, and neurological deficits.
Investigations	- **Direct detection:** Darkfield microscopy, PCR. - **Serologic tests:** Nontreponemal (RPR, VDRL) for screening; Treponemal (FTA-ABS, TPPA) for confirmation. - **CSF analysis:** For suspected neurosyphilis.
Interpretation of Serology	- **Positive nontreponemal + treponemal test:** Active or treated syphilis. - **Negative nontreponemal test + positive treponemal test:** Previous or early infection. - **Negative both tests:** No syphilis.

Aspect	Details
Management	**Early Syphilis:** IM Penicillin G benzathine (2.4 million units single dose). **Late Syphilis:** Penicillin G benzathine (2.4 million units weekly for 3 weeks). **Neurosyphilis:** IV penicillin G every 4 hours for 10–14 days; ceftriaxone if allergic. **Contacts:** Identify, evaluate, and treat all sexual contacts.
Treatment Alternatives	Doxycycline, ceftriaxone for patients allergic to penicillin.



Chancre of the glans penis in primary syphilis

Classical palm lesions of secondary syphilis



Jarisch-Herxheimer reaction

- **Acute febrile illness with headache, myalgia, chills and rigours starting within 12 hours of the first dose of treatment.**
- Due to the release of endotoxins following bacterial death
- Occurs in ~50% of patients with primary syphilis, **90% with secondary syphilis** and 25% with early latent syphilis.
- Occurs in **Lyme disease** and **Q fever**.
- Management → reassurance and paracetamol for symptom control, **resolve within 24 hours**

Chlamydia genitourinary infections

Pathogenesis: *Chlamydia trachomatis*, is an obligate intracellular pathogen.

Incubation period: 7-21 days

Epidemiology: *Chlamydia* is the most prevalent sexually transmitted infection in the UK. Approximately 1 in 10 young women in the UK have *Chlamydia*.

Features

- **Asymptomatic** in the majority of the patient
- **Women:** cervicitis (muco-purulent discharge, postcoital bleeding, dyspareunia), **rectal infection** (associated with 75% of urogenital chlamydia) and complications (PID, ↑ risk of ectopic pregnancies, infertility and perihepatitis (Fitz-Hugh-Curtis syndrome).
- **Men:** urethritis (urethral discharge, dysuria), acute epididymitis, chronic prostatitis and **proctitis** (in men who have sex with men → anorectal pain, discharge, and tenesmus)

Diagnosis

- **The investigation of choice → Nuclear acid amplification tests (NAATs)** of vaginal swabs for females or urine for males or rectal swabs to diagnose chlamydial proctitis.
- **Test for Neisseria gonorrhoeae** (N.gonorrhoeae and C. trachomatis causes **similar** clinical features and also commonly **coexists**).
- Screen for other sexually transmitted infections (STIs), including HIV.

Management

- **1st line: Doxycycline 100mg bd for 7 days**
- **2nd line:** Azithromycin (**1 g** single dose): If doxycycline cannot taken and also **preferred in pregnancy**.
- Patients are advised to avoid sexual contact for 7 from starting medication
- Treatment of sex partners **(treat then test)**
  - ⇨ Any sex partner within 60 days of infection
  - ⇨ The most recent sex partner if >60 days from infection

Gonorrhoea

Definition

- Gonorrhoea is the UK's second most common bacterial STI after chlamydia. **Caused by** Neisseria gonorrhoeae, gram-negative, intracellular, aerobic, diplococci. **Transmitted by** Sexual (oral, genital, or anal) and perinatal

Risk factors: multiple sexual partners in recent months, known partner with gonorrhoea, drug use, prior STI, and men who have sex with men.

Features

- **Urogenital:**
  - ⇨ Females: asymptomatic in 70%. Cervicitis (vaginal discharge), Urethritis (dysuria)
  - ⇨ Males: urethritis (urethral discharge, dysuria), Epididymitis (scrotal pain and swelling)
- **Extragenital:** Conjunctivitis, Pharyngitis, Proctitis (anorectal pain, bleeding, and discharge)

Complications

- **Pelvic inflammatory disease**
- **Fitz-Hugh-Curtis syndrome** (inflammation of liver capsule, ascending spread from PID in females)
- **Disseminated gonococcal infection** (haematogenous spread from mucosal infection)
  - ⇨ Arthritis-dermatitis syndrome (a triad of polyarthralgia, tenosynovitis and dermatitis)
  - ⇨ Purulent gonococcal arthritis: septic arthritis (not to be confused with reactive arthritis)
  - ⇨ Rare: endocarditis, meningitis, and osteomyelitis

Diagnosis

- **Nucleic Acid Amplification Test (NAAT)** using vaginal or rectal swab and first-catch urine in males (**the test of choice, more sensitive than culture**). Patients can self-swab
- **Microscopic examination of urethral swab for urethritis in males:** polymorphonuclear leukocytes with intracellular gram-negative diplococci on Gram stain (diagnostic)
- **Culture:** limited role for diagnosis, but indicated if NAAT unavailable or to assess antibiotic susceptibilities when resistance is suspected.
- **Screen for other sexually transmitted infections (STIs),** including HIV, chlamydia, and syphilis

Gonorrhoea Management

Management Approach	Details
1st Line Treatment	Ceftriaxone 1 g IM (single dose). Most patients with penicillin allergy can still use ceftriaxone.
2nd Line Treatment	Cefixime + high-dose azithromycin (2 g PO) + Gentamicin 240 mg IM (as two 3 mL injections). Reserved for patients with urogenital or anorectal infections who cannot take ceftriaxone.
Chlamydia Coinfection	Presumptive treatment: Doxycycline 100 mg PO twice daily for 7 days unless excluded by microbiological testing.
Disseminated Gonococcal Infection	IV Ceftriaxone 1 g daily for 7 days. In septic arthritis, continue ceftriaxone for 7-14 days with joint drainage.

Management Approach	Details
Treatment of Sexual Partners	Treat any sexual partner from the last 60 days or the most recent partner if sexual contact occurred >60 days ago.

Comparison of Gonorrhoea vs. Chlamydia

Feature	Gonorrhoea	Chlamydia
Pathogen	*Neisseria gonorrhoeae* (bacterium)	*Chlamydia trachomatis* (bacterium)
Mode of Transmission	Sexual contact (oral, vaginal, anal)	Sexual contact (oral, vaginal, anal)
Incubation Period	2-14 days	7-21 days
Symptoms in Men	Urethral discharge (yellow/green), dysuria	Dysuria, milder discharge (clear/white)
Prevalence	More common in urban areas	More common overall, especially in young adults
Complications	Pelvic inflammatory disease (PID), infertility, epididymitis, disseminated gonococcal infection	PID, infertility, ectopic pregnancy, epididymitis
Diagnosis	NAAT (nucleic acid amplification test) from urine or swabs	NAAT from urine or swabs
Treatment	**First line**: Ceftriaxone 500 mg IM + azithromycin 1 g PO (single dose)	**First line**: Doxycycline 100 mg PO twice daily for 7 days
Antibiotic Resistance	High (requires combination therapy)	Rare resistance

More commonly patients present with co-infection with *Chlamydia trachomatis*.

Toxoplasmosis

Cause: Toxoplasma gondii, an intracellular protozoan parasite.

Transmission: the usual animal reservoir is the cat, commonly Kittens (mature cats are less likely to secrete toxoplasma) transmitted to human by one of three routes:

- **Fecal-oral route (most common):** Ingestion of cysts in **undercooked meat** (Sheep and cattle eat food contaminated with soil contaminated by kitten faeces; and humans ingest the organisms **from undercooked meat.** Or ingestion of oocysts in cat feces (from contaminated fruits or vegetables)
- **Vertical transmission** from an infected mother to her fetus (transplacental) → **congenital toxoplasmosis.**
- **Organ transplantation** from an infected donor.

Risk factors: HIV (if CD4+ count < 100 cells/Ml):

Pathophysiology

- ~ 30% of the worldwide population is infected. ↓immunity (eg, HIV, CD4+ count <100cells/microL.) → **reactivation** of the disease.
- Oocysts of Toxoplasma gondii (via GI tract, lung or broken skin) → release trophozoites → migrate to the eye, brain and muscle.

Feature

- Immunocompetent patients
  - ⇨ Most common: asymptomatic.
  - ⇨ Less common: **features resembling infectious mononucleosis** (fever, malaise, bilateral, symmetrical, nontender cervical adenopathy).
  - ⇨ Rare: pneumonitis, myocarditis, polymyositis, hepatitis, posterior uveitis, or encephalitis.
- Immunocompromised patients: (HIV and a CD4 count <100 cells/microL.): **most commonly Meningio-encephalitis → Fits**

Congenital toxoplasmosis presents with a classic triad of:
1. **Chorioretinitis**,
2. Hydrocephalus and
3. **Intracranial calcifications**.

Investigation

- **Serology testing** for anti-toxoplasma IgM and IgG antibodies via **ELISA**
  - ⇨ IgM: positive within first week of acute infection
  - ⇨ IgG: positive 2 weeks following infection and remains positive for life
- **If positive IgG alone** → Polymerase Chain Reaction testing (PCR), or histopathology (reveals →Tachyzoites: crescent-shaped or cysts): IgG alone cannot distinguish active from past infection.
- **Brain MRI** for HIV patients who present with fits → multiple ring-enhancing **lesions.**

Treatment

- **Immunocompetent** → self-limiting (not require treatment)
- **Severe infections** (pneumonitis, myocarditis, meningoencephalitis, posterior uveitis, or polymyositis) **or immunosuppressed patient:**
  - ⇨ 1st line: **Pyrimethamine plus sulfadiazine for 6 weeks** (folinic acid, also known as **leucovorin**, should be added to prevent pyrimethamine- associated hematologic toxicity).
  - ⇨ 2nd line: (if sulfonamide are not tolerated): pyrimethamine plus clindamycin.
- **Patients with HIV:** add antiretroviral therapy (ART) for immune recovery.

Prevention

- Prophylaxis in immunocompromised patients when **CD4 count** <100 cells/μL : Trimethoprim-sulfamethoxazole is the drug of choice
- To reduce risk of congenital infection (**maternal-fetal transmission**)
  - ⇨ Non-infected pregnant: **avoid contact with cat litter**
  - ⇨ Infected **pregnant** → **spiramycin** (a macrolide antibiotics inhibit bacterial growth by targeting the 50S ribosomal subunit. ↓risk of fetopathy by more than 50%.

Acute upper respiratory tract infections: Overview

Condition	Pathogens	Distinct Features & Findings	Treatment
Common Cold	Rhinovirus	No focal features	Symptomatic care only
Influenza	Influenza virus	Chills, Myalgias, High fever	**Oseltamivir**: 75 mg twice daily for 5 days (only if high risk or severe case)
COVID-19	SARS-CoV-2	Loss of smell/taste, SOB	**Remdesivir**: 200 mg IV on day 1, then 100 mg for 4 days (severe cases) **Dexamethasone**: 6 mg once daily for 10 days (if hypoxic)
Sinusitis	Rhinovirus, S. pneumoniae, H. influenzae	Facial pain, Tenderness on palpation	If bacterial: **Amoxicillin**: 500 mg TID for 5-7 days Alternative: **Doxycycline** 200 mg day 1, then 100 mg daily for 4 days
Tonsillitis	Rhinovirus, S. pyogenes	Sore throat, Inflamed tonsils	**Phenoxymethylpenicillin**: 500 mg 2-4 times daily for 10 days Alternative: **Clarithromycin** 250-500 mg BID for 5 days
Pharyngitis	Rhinovirus, S. pyogenes	Sore throat, FeverPAIN criteria positive	If bacterial: **Phenoxymethylpenicillin**: 500 mg 2-4 times daily for 10 days Alternative: **Clarithromycin** 250-500 mg BID for 5 days
Laryngitis	Rhinovirus, S. pneumoniae, H. influenzae	Hoarseness, Barking cough	**Amoxicillin**: 500 mg TID for 5-7 days (if bacterial cause suspected)
Epiglottitis	H. influenzae, S. pneumoniae, S. pyogenes	Drooling, Stridor, Tripod position	**Ceftriaxone**: 1-2 g IV daily **Dexamethasone**: 6 mg IV daily (for airway swelling)
Croup	Parainfluenza virus	Barking cough, Stridor	**Dexamethasone**: 0.15 mg/kg orally (once) Severe cases: **Nebulized epinephrine**

Influenza

Definition

- A viral infection caused by the influenza virus, affecting the respiratory system.
- It typically spreads through respiratory droplets from coughing or sneezing.

Pathophysiology

- The influenza virus infects epithelial cells of the respiratory tract.
- This leads to local inflammation, increased mucus production, and systemic immune activation, causing fever and malaise.

'ypes

1. **Influenza A** – Causes pandemics; has multiple subtypes (H1N1, H3N2).
2. **Influenza B** – Generally causes milder outbreaks.
3. **Influenza C** – Mild infections, rarely epidemic.
4. **Influenza D** – Primarily affects cattle, not known to infect humans.

Feature	Influenza A	Influenza B
'revalence	More common, responsible for annual pandemics and most influenza cases globally	Less common, often associated with localised outbreaks
ienetic iversity	Multiple subtypes (H1N1, H3N2, etc.) due to antigenic shift and drift	Less genetic variability, only antigenic drift
andemics and pidemics	Responsible for pandemics and widespread epidemics	Causes seasonal epidemics but not pandemics
lost Range	Infects humans, birds, pigs, and other animals	Primarily infects humans
everity	Often more severe symptoms and complications	Usually milder, but can still cause severe illness in high-risk groups

:linical Features

- **General symptoms:** Sudden onset of fever, chills, muscle aches, fatigue, sore throat, cough, and runny nose.
- **Gastrointestinal symptoms:** Nausea, vomiting (more common in children).
- **Complications:**
  - Viral pneumonia
  - Secondary bacterial infections (e.g., pneumonia caused by *Streptococcus pneumoniae*)
  - Exacerbation of chronic conditions (e.g., asthma, COPD)

iagnosis

- **Clinical diagnosis**: Based on symptoms and exposure during an outbreak.
- **Lab tests**:
  - Rapid influenza diagnostic tests (RIDTs)
  - PCR testing for more precise detection of viral RNA

reatment

1. **Antiviral Therapy**: Recommended within 48 hours of symptom onset.
   - **Oseltamivir**: 75 mg twice daily for 5 days (first-line)
   - **Zanamivir**: Inhaled, 10 mg twice daily for 5 days
   - **Peramivir**: IV, for severe cases
2. **Symptomatic Management**:
   - Paracetamol or ibuprofen for fever and body pain
   - Hydration and rest

'revention

- **Annual Influenza Vaccine**:
- **NICE guidance recommends prophylaxis with oseltamivir within 48 hours of close contact with a patient infected with influenza for high-risk patients.**

Complications

- **Respiratory failure**: Especially in elderly or immunocompromised.
- **Myocarditis and encephalitis**: Rare, but severe complications.
- **Guillain-Barré Syndrome**: Rare neurological complication linked to infection or vaccination.

Infectious mononucleosis (glandular fever)

Category	Details
Definition	Infectious mononucleosis (IM), also known as glandular fever, is a viral infection primarily caused by the Epstein-Barr virus (EBV).
Transmission	Spread through saliva (often called the "kissing disease"). Less commonly transmitted via blood or organ transplant.
Incubation Period	4-6 weeks.
Clinical Features	- **Fever, sore throat, and lymphadenopathy** (particularly cervical nodes). - **Fatigue and malaise** (can persist for weeks to months). - **Splenomegaly** (50% of cases) and hepatomegaly. - **Pharyngitis with tonsillar exudates**. - **Rash**: May develop, especially if treated with amoxicillin.
Complications	- **Hepatitis and jaundice**. - **Splenic rupture** (rare but serious). - **Airway obstruction** from tonsillar swelling. - **Autoimmune hemolytic anemia and thrombocytopenia**. - **Neurological complications**: Guillain-Barré syndrome, meningitis, encephalitis.
Diagnosis	- **Monospot test (heterophile antibody test):** Positive after 1 week of illness. - **EBV-specific antibodies:** Used if Monospot is negative. - **Blood tests:** Lymphocytosis with >10% atypical lymphocytes. - **Liver function tests:** Elevated transaminases.
Management	- **Supportive care:** Rest, hydration, and analgesics (e.g., paracetamol or NSAIDs). - **Corticosteroids:** For severe complications such as airway obstruction, thrombocytopenia or hemolytic anaemia. - **Avoid contact sports** for at least 3-4 weeks to prevent splenic rupture.

Parvovirus B19

Category	Details
Definition	Parvovirus B19 is a small, non-enveloped, single-stranded DNA virus from the Parvoviridae family. It primarily infects erythroid progenitor cells.
Transmission	Spread through respiratory droplets, blood transfusion, or vertically from mother to fetus.
Incubation Period	4-14 days (up to 21 days in some cases).

Category	Details
Clinical Features	- **Erythema infectiosum (Fifth disease):** Slapped-cheek rash, low-grade fever, fatigue. - **Arthropathy:** Symmetrical arthritis or arthralgia in adults (mimics rheumatoid arthritis). - **Transient aplastic crisis:** Occurs in individuals with hemolytic anemia (e.g., sickle cell disease). - **Fetal infection:** Can cause hydrops fetalis and fetal loss.
High-Risk Groups	Pregnant women, individuals with chronic hemolytic disorders, and immunocompromised patients.
Diagnosis	- **Serology:** Presence of anti-parvovirus B19 IgM antibodies indicates recent infection. - **PCR:** Detects viral DNA (useful in immunocompromised individuals).
Complications	- Transient aplastic crisis. - Hydrops fetalis and fetal death. - Chronic anemia in immunocompromised patients. - Myocarditis, glomerulonephritis (rare).
Management	- **Supportive care** (most infections are self-limiting). - **Blood transfusion** for transient aplastic crisis. - **Intravenous immunoglobulin (IVIG):** For chronic anemia in immunocompromised patients. - **Monitoring:** Serial ultrasounds in pregnant women exposed to B19 to assess for fetal hydrops.

Visceral leishmaniasis (kala-azar)

Cause	Leishmania donovani (an intracellular protozoa, invade and replicate within host macrophages)
Transmission	By phlebotomine sand flies
Incubation period	Usually 2 - 6 months (but can range from a few weeks to several years.)

Features

- Many patients are asymptomatic
- Fever, sweating, rigor, malaise, and weight loss
- Lymphadenopathy, massive splenomegaly and hepatomegaly
- Ascites and edema
- Grey skin - 'kala-azar' means black sickness in Hindi.

Investigations

- **General:**
  - ⇨ CBC: Pancytopenia secondary to hypersplenism, Hemolytic anaemia
  - ⇨ LFT: ↑ Transaminases, ↓ Albumin, ↑ Total protein
  - ⇨ Inflammatory markers: ↑ ESR
  - ⇨ Serum protein electrophoresis: Polyclonal hypergammaglobulinaemia

- **Confirmatory test**
  - ⇨ **Tissue aspirate or biopsy for histopathology and culture of material:** bone marrow (preferred), lymph node → **visualisation of the parasite (amastigote form)**
  - ⇨ **PCR** can be used to detect the parasite in in tissue or blood.
  - ⇨ **Serologic testing** (direct agglutination test: detect anti-leishmanial antibodies): supports the diagnosis if positive (but may be falsely negative in immunocompromised patients and remain positive up to several years after cure and therefore cannot be used to detect relapse).

Treatment

Treatment

- **Recommended (1st line)**
  - Liposomal amphotericin B (IV 3 mg/kg once daily on days 1–5, 14, and 21)
- **Other options**
  - Antimonial drugs (sodium stibogluconate) Not preferred now due to widespread high-level resistance. Side effects include cardiac arrhythmias and acute pancreatitis.

Types of leishmaniasis

Cutaneous leishmaniasis	❑ <u>Caused by</u> Leishmania tropica or Leishmania mexicana ❑ <u>Present with</u> ulcers or nodules, crusted lesion at site of bite, usually heal spontaneously (but slowly in immuncompetent individuals) with resultant disfiguring scars.
Muco-cutaneous leishmaniasis	❑ <u>Caused by</u> Leishmania braziliensis ❑ <u>Present with</u> skin and destructive mucosal ulcerative lesions which may involve mucosae of mouth, nose, pharynx and larynx. It is not self-healing.
Post kala-azar dermal leishmaniasis	❑ A late complication of treated visceral leishmaniasis characterized by the formation of dermal lesions (macular, maculo-papular or nodular rash) containing amastigotes and highly infectious

Leptospirosis

Definition

- A zoonotic infection caused by Leptospira, a motile, aerobic spirochetes, most common in tropical regions.

Transmission

- Urine, blood, or tissue of an infected animal (most commonly rats) → Environmental contamination (e.g., water contaminated with urine of infected animals) → Leptospira enter via broken skin or exposed mucous membranes (e.g., conjunctiva, oral mucosa)

Risk factors

- Occupational contact with animals (e.g., **farmers** or sewage workers)
- Freshwater swimming

Features

- **Anicteric leptospirosis (mild):**
  - ⇨ Nonspecific: fever, rigors, myalgias (especially in the calves and lower back), and headache. Lymphadenopathy, hepatosplenomegaly
  - ⇨ Specific → conjunctival suffusion (bilateral diffuse reddening of the conjunctivae without exudates): occurs in > 50%.
  - ⇨ Aseptic meningitis and uveitis can complicate this phase.
- **Icteric leptospirosis (severe) (Weil's disease):** rapidly progressive multiple organ failure (occurs in 5 to 10%): **hepato-renal failure** (jaundice), hemorrhagic diathesis (e.g., hemoptysis, purpura, melena), pulmonary hemorrhage, cardiac inflammation (e.g., myocarditis, pericarditis).

Diagnostic tests

- Polymerase chain reaction (PCR) of blood or urine
- Serologic test (IgM and IgG)
- Blood and urine culture
- CSF for PCR (for patients with meningitis).

Treatment

- **Mild leptospirosis:** doxycycline, azithromycin (preferred as also effective for rickettsial infections, which is undistinguishable from leptospirosis) or amoxicillin.
- **Severe leptospirosis:** IV penicillin, or 3rd generation cephalosporins (lack effect against rickettsial infection, so not used unless it is ruled out) or doxycycline.

Lyme disease

Aspect	Details
Definition	Lyme disease is a tick-borne infection caused by *Borrelia burgdorferi*, transmitted through bites of infected *Ixodes ricinus* ticks. It is the most common tick-borne disease in the US and Europe.
Features	**Early Localised Lyme Disease:** Erythema migrans (80%) forms a bulls-eye lesion at the bite site; systemic symptoms include fever, malaise, and arthralgia. **Early Disseminated Lyme Disease:** Weeks to months post-infection; may present with heart block, myocarditis, cranial nerve palsies, meningitis, and polyarthritis. **Late Lyme Disease:** Develops months to years later, often causing arthritis, or acrodermatitis chronica atrophicans (skin condition) on the extensor surfaces; rare neurological issues like polyneuropathy or encephalomyelitis.
Investigation	**Serology (ELISA):** Detects IgM and IgG antibodies against *Borrelia burgdorferi*. This is the first-line diagnostic test.
Management	**Early Disease:** Doxycycline for 2–3 weeks; amoxicillin as an alternative (e.g., in pregnancy). **Disseminated Disease:** Ceftriaxone.
Treatment complication	**Jarisch-Herxheimer Reaction:** Fever, rash, and tachycardia may occur after initiating antibiotic therapy, more commonly associated with syphilis but also seen in Lyme disease.

Lyme disease features = FACE (Facial nerve palsy, Arthritis, Carditis, Erythema

Bilateral facial weakness can occur with Lyme disease, myasthenia gravis, sarcoidosis and bilateral Bell's palsy.

Lymphadenopathy

Definition

- Abnormal enlargement of lymph nodes (>1 cm), due to infection, inflammation, or malignancy.

Classification

1. **Localized Lymphadenopathy**: Involves a single lymph node region.
2. **Generalized Lymphadenopathy**: Involves multiple lymph node regions across the body.

Causes

Category	Examples
Infectious	Bacterial (TB, syphilis), Viral (HIV, EBV, CMV), Fungal (histoplasmosis)
Malignancies	Lymphomas, Leukaemias, Metastatic cancers
Autoimmune	Systemic lupus erythematosus (SLE), Rheumatoid arthritis
Drug-Induced	Phenytoin, Allopurinol
Miscellaneous	Sarcoidosis, Kikuchi disease

Causes of localised lymphadenopathy

Painful	Painless
➲ Skin infection ➲ Pharyngitis ➲ Oral/genital herpes ➲ Cat scratch disease (typically cervical or axillary adenopathy) ➲ Lymphogranuloma venereum (buboes) ➲ Chancroid ➲ Kawasaki disease (usually unilateral cervical lymphadenopathy) ➲ Mononucleosis (bilateral cervical lymphadenopathy) ➲ Rubella (especially postauricular nodes), mumps	➲ Tuberculosis, sarcoidosis ➲ Systemic lupus erythematosus ➲ Metastases ➲ Residual lymph nodes after overcoming an infection

Causes of generalised lymphadenopathy

Defined as the enlargement of more than two noncontiguous lymph node groups.

Painful	Painless
Viral infections ➲ CMV ➲ HIV ➲ Mumps, measles, rubella ➲ Varicella **Bacterial infections** ➲ Listeriosis ➲ Brucellosis ➲ Syphilis **Parasitic infections** ➲ Malaria ➲ Schistosomiasis ➲ Visceral leishmaniasis ➲ Toxoplasmosis	**Malignancy** ➲ **Malignant lymphoma** (NHL, Hodgkin lymphoma) ➲ **Leukaemia** **Autoimmune** ➲ Circulating immune complexes (due to medication or allergies): **phenytoin and to a lesser extent allopurinol, isoniazid** ➲ Sjogren syndrome **Others** ➲ Lysosomal storage disease: Gaucher disease, Niemann-Pick disease, Fabry disease ➲ Hyperthyroidism ➲ Amyloidosis ➲ Sarcoidosis ➲ Tuberculosis

Benign VS malignant lymphadenopathy

Characteristics	Likely benign or inflammatory cause	Likely malignant or mycobacterial cause
Pain	Tender	Non-tender
Consistency	Soft	Hard
Fixation	Mobile	Fixed
Location	Cervical (anterior to the sternocleidomastoid muscle), inguinal	Cervical (dorsal to the sternocleidomastoid muscle), supraclavicular
Progression	Acute enlargement without long-term progression	Slow development combined with progressive enlargement

Common Diagnostic Features by Cause

- **Infection**: Painful, tender lymph nodes, often with systemic symptoms (fever, malaise).
- **Malignancy**: Hard, fixed, non-tender nodes, often supraclavicular.
- **Autoimmune**: Painless lymphadenopathy with associated autoimmune symptoms (e.g., rash, arthritis).
- **Drug Reaction**: Resolves with drug discontinuation.

Investigations

- **Laboratory Tests**:
  - Complete Blood Count (CBC) to assess infection or malignancy.
  - ESR/CRP for inflammation.
  - Serology: EBV, HIV, CMV.
  - Autoimmune markers (ANA, RF).
- **Imaging**:
  - Ultrasound: Distinguish between solid vs. cystic nodes.
  - CT/MRI: Evaluate deep-seated lymph nodes.

- **Biopsy**:
  - Fine-needle aspiration (FNA) or excisional biopsy for definitive diagnosis in suspicious cases.

Management

1. **Infectious Causes**: Antibiotics or antivirals (as indicated).
2. **Malignancy**: Chemotherapy, radiotherapy, or surgery.
3. **Autoimmune Disease**: Immunosuppressants (e.g., corticosteroids).
4. **Drug-Induced**: Discontinue the offending drug.
5. **Supportive Care**: Analgesics for pain and anti-inflammatories if needed.

Key Points

- Persistent lymphadenopathy >4 weeks or significant enlargement (>2 cm) warrants further investigation.
- Supraclavicular lymphadenopathy is often associated with malignancy.

Malaria

Definition: a tropical infectious disease caused by Plasmodium parasites. Transmitted through the bite of an infected female Anopheles mosquito.

Classification based on plasmodium species

P. falciparum	➲ **The most common cause of severe malaria** ➲ dominant in Africa ➲ only trophozoite-ring forms and gametocytes are usually seen. ➲ incubation period 7 to 30 days.
P. vivax	➲ The **most common cause of non-falciparum malaria** ➲ often found in Central America and the Indian Subcontinent ➲ **have a liver hypnozoite stage which can cause repeated relapses.** ➲ **incubation period of P. vivax can go up to six months or more** ➲ **The Duffy antigen on RBCs acts as a receptor for P. vivax, facilitate the entry of P. vivax in to RBCs (Duffy negative individuals are therefore resistant to this strain)** ➲ **causes milder disease**
P. ovale	➲ quite rare, typically comes from Africa ➲ **have a liver hypnozoite stage which can cause repeated relapses.** ➲ **all stages of the parasite and not just trophozoites and gametocytes are visible in the peripheral blood** ➲ **cause milder disease**
P. malariae	Rare. cause milder disease Incubation period: occasionally months to years
P. knowlesi	found in Southeast Asia and can cause severe malaria; possibly zoonotic shorter incubation period : 9 to 12 days and shorter Cycle in red cell (24 hours)

Classification based on severity

1) Uncomplicated malaria (No features of severe malaria)
2) **Severe malaria**

Features of severe malaria	
Clinical findings	**Laboratory findings**
➲ **General:** prostration ➲ **CNS:** hallucinations, confusion, impaired consciousness, seizures, coma ➲ **Cardiac:** shock (e.g., hypotension, capillary refill time ≥ 3 seconds), heart failure ➲ **Pulmonary:** respiratory distress, pulmonary edema, ARDS ➲ **Renal:** flank pain, oliguria, hemoglobinuria, acute kidney injury ➲ **Gastrointestinal:** jaundice ➲ **Hematopoietic:** significant bleeding	➲ **Severe anemia:** < 7 g/dL in adults, < 5 g/dL in children ➲ **Hypoglycemia:** < 40 mg/dL ➲ **Acidosis** (with or without lactemia): base deficit > 8 meq/L or bicarbonate < 15 meq/L ➲ **Hyperlactatemia:** lactate > 5 meq/L ➲ **Acute kidney injury:** creatinine > 3 mg/dL or urea > 20 mmol/L ➲ **Hyperbilirubinemia:** bilirubin > 3 mg/dL ➲ **Hyperparasitemia** > 2% in low intensity transmission areas or >5% in high intensity transmission areas.

Features

- fever, headache, malaise
- GIT: nausea , vomiting , diarrhoea, abdominal pain , jaundice, hepatosplenomegaly
- CNS: hallucinations, confusion, impaired consciousness, seizures, coma
- ***Plasmodium malariae***: is associated with **nephrotic syndrome**

Investigations

- Diagnostic:
  - ⇨ Microscopic examination of thick and thin blood smears (gold standard)
    - Thick blood smear: high sensitivity; best initial test
    - Thin blood smear: lower sensitivity, high specificity; confirmatory test → detect Plasmodium species and calculate parasitemia → classify severity and monitor response to therapy.
  - ⇨ Antigen detection test (more rapid but less sensitive)
- General
  - ⇨ CBC: Thrombocytopenia
  - ⇨ Hemolytic anemia: ↓ Hb, ↓ haptoglobin, ↑ LDH, ↑ indirect bilirubin, ↑ reticulocytes
  - ⇨ Hypoglycemia and AKI can occur in severe malaria.
  - ⇨ Urinalysis: Hemoglobinuria may occur with intravascular hemolysis.

Management

- **Uncomplicated falciparum malaria**
  - ⇨ **First-line therapy:** artemisinin-based combination therapies (ACTs) such as artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

- **Severe falciparum malaria**
  - ⇨ 1st line: intravenous artesunate (2.4 mg/kg IV every 12 hours for 3 doses).
    - Repeat malaria parasite density after 3rd dose of artesunate. If > 1%: continue IV artesunate, if ≤ 1%: switch to oral antimalarials: Artemether-lumefantrine (preferred)
  - ⇨ 2nd line: intravenous quinine: **Hypoglycaemia is an important side effect of quinine**
  - ⇨ **Artemisinins are the first line in pregnancy** in the 2nd and 3rd trimesters. In 1st trimester, both artesunate and quinine are considered treatment options.
  - ⇨ **Exchange transfusion:** if parasite count > 10%
- **Non-falciparum malaria**
  - ⇨ often chloroquine-sensitive; more recently, Plasmodium vivax is becoming increasingly resistant to chloroquine.
  - ⇨ Ovale or vivax malaria: chloroquine should be followed by primaquine to destroy liver hypnozoites and prevent relapse (all individuals should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency, as primaquine may cause haemolysis in those without the enzyme.
- **Recurrent infection**
  - ⇨ **Treatment failure:** lack of resolution of fever and parasitemia (or recurrence of these findings) within 28 days of treatment → give alternative ACT therapy
  - ⇨ **Reinfection:** fever and parasitemia >28 days following treatment → treatment with a first-line ACT

Quinine toxicity (cinchonism)

- **Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed, dry skin and abdominal pain.**
- **Complications: cardiac arrhythmia (common), permanent blindness, and renal failure.**
- **Management: supportive.**

Malaria prophylaxis

- 75% of malaria in patients returning from endemic countries are caused by the potentially fatal Plasmodium *falciparum* protozoa.
- UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

Drug	Side-effects + notes	Time to begin before travel	Time to end after travel
Atovaquone + proguanil (Malarone) ➲ used for areas with high resistance against other drugs. ➲ **Avoid in pregnancy** unless essential. If taken then folate supplementation should be given	**GI upset**	**1 - 2 days**	**7 days**
Chloroquine	Headache Contraindicated in epilepsy Taken weekly	1 week	4 weeks
Doxycycline ➲ **the safest option with less resistance** ➲ contraindicated in pregnancy ➲ for age > 12 years	**Photosensitivity** **Oesophagitis**	**1 - 2 days**	**4 weeks**
Mefloquine (Lariam)	Dizziness Neuropsychiatric disturbance **Contraindicated in epilepsy and mental illnesses** Taken weekly	2 - 3 weeks	4 weeks
Proguanil (Paludrine) ➲ In pregnancy, folate supplementation (5mg od) should be given		1 week	4 weeks
Proguanil + chloroquine	See above	1 week	4 weeks

Partial resistance against malaria

- Carriers of sickle-cell mutation
- Individuals with either certain Duffy antigens or no Duffy antigens are resistant to P. vivax and P. knowlesi
- Other hemoglobinopathies (e.g., thalassemia, HbC)
- Infection with malaria subsequently leads to the development of specific Plasmodium antibodies that result in partial immunity for a limited amount of time (less than a year)

Measles

Aspect	Details
Definition	A highly contagious viral infection caused by the measles virus (a paramyxovirus). Primarily affects children but can occur at any age.
Transmission	Airborne droplets from coughing, sneezing, or direct contact with nasal or throat secretions. Highly contagious, with a secondary attack rate of up to 90% in non-immune individuals.
Incubation Period	10-14 days from exposure to onset of symptoms.
Clinical Features	1. **Prodromal Phase** (2-4 days): High fever, cough, coryza (runny nose), conjunctivitis (3 C's). 2. **Koplik Spots**: Small white spots on the buccal mucosa, pathognomonic of measles. 3. **Rash**: Erythematous maculopapular rash starts behind ears and face, spreading downwards over the body, fading after 5-6 days.
Complications	Otitis media, pneumonia, diarrhoea, encephalitis (1 per 1,000 cases), subacute sclerosing panencephalitis (SSPE). More severe in malnourished or immunocompromised individuals.
Diagnosis	Clinical presentation; confirm with **measles-specific IgM** in serum or **PCR** of nasopharyngeal swabs.
Treatment	Supportive care: Antipyretics, fluids, and treatment of secondary infections. **Vitamin A supplementation** recommended, especially in children with malnutrition or severe disease.
Prevention	MMR vaccine (Measles, Mumps, Rubella) given at 12-15 months, with a second dose at 4-6 years.
Isolation Precautions	Infected individuals should be isolated for 4 days after rash onset to prevent spread.
Management of Contacts	Administer **MMR vaccine** within 72 hours of exposure or **immunoglobulin** within 6 days to susceptible contacts.

Rubella (German measles)

Rubella (German Measles)	Details
Definition	A mild viral infection caused by the rubella, **RNA virus,** part of the togavirus family
Clinical Features	Fever, rash, and lymphadenopathy.
Transmission	Airborne droplets or direct contact with an infected person.
Complications	Severe in pregnancy: fetal death, premature delivery, and congenital abnormalities (hearing loss, cardiac defects, developmental delay).
Diagnosis	Initial: Rubella-specific IgM serology. Confirmatory: PCR from throat or nasal swab.
Treatment	Supportive care; no specific antiviral therapy.
Management of Contacts	Isolation of infected individuals for 7 days post-rash onset. If immune, no precautions required.
Prevention	Vaccination through the MMR vaccine.
Unique Findings	"Positive rubella haemagglutination inhibition (HAI) with negative IgM" suggests recent infection or vaccination; requires retesting.

Parotid swelling

Causes

1. **Infectious Causes:**
   - **Viral infections:** Mumps (most common cause), HIV, influenza, coxsackievirus
   - **Bacterial infections:** *Staphylococcus aureus*, Streptococcus (acute bacterial parotitis)
   - **Recurrent parotitis of childhood** (self-limiting, inflammatory)
2. **Non-infectious Causes:**
   - **Autoimmune:**
     - Sjögren's syndrome (chronic bilateral swelling with dry eyes/mouth)
     - Sarcoidosis
   - **Obstruction:** Sialolithiasis (salivary stones blocking ducts)
   - **Neoplasms:** Benign (pleomorphic adenoma) or malignant (mucoepidermoid carcinoma) tumors
   - **Drug-induced:** Antihistamines, diuretics, and anticholinergics (reduce saliva flow)
3. **Metabolic and Systemic Causes:**
   - Diabetes mellitus
   - Alcoholism (sialadenosis)
   - Malnutrition or anorexia

Clinical Features

- **Unilateral Swelling:** Often indicates bacterial infection or neoplasm
- **Bilateral Swelling:** Suggests viral infection, autoimmune disease, or systemic causes
- **Pain:** Seen in acute infections or sialolithiasis
- **Dry mouth and eyes:** Common in Sjögren's syndrome
- **Fever and erythema:** Indicate infection
- **Firm or hard mass:** Suspect malignancy

Complications

- **Chronic infection or abscess formation**
- **Malignant transformation of benign neoplasms**
- **Xerostomia** (dry mouth) in autoimmune or systemic diseases
- **Facial nerve injury** (if tumor affects or surgery involves the parotid gland)

Investigations

1. **Blood tests:**
   - Raised amylase (mumps)
   - Autoimmune markers (e.g., ANA, anti-SSA, anti-SSB for Sjögren's)
   - HIV serology
2. **Imaging:**
   - **Ultrasound:** To assess for abscesses or sialolithiasis
   - **CT/MRI:** For deeper gland evaluation and tumor assessment
   - **Sialography:** To identify ductal stones or strictures
3. **Biopsy or Fine Needle Aspiration Cytology (FNAC):**
   - Indicated in suspected neoplasms or persistent swelling

Management

1. **Infectious Causes:**
   - **Viral (e.g., mumps):** Supportive care (hydration, analgesia)
   - **Bacterial:**
     - Empiric antibiotics (e.g., *Amoxicillin-clavulanate*)
     - Warm compresses and massage
     - Surgical drainage for abscess

2. **Obstruction (Sialolithiasis):**
   - Hydration and sour candies to stimulate saliva flow
   - Surgical removal if stone does not pass spontaneously
3. **Autoimmune (Sjögren's Syndrome):**
   - Symptomatic treatment with artificial saliva and tears
   - Immunosuppressants (e.g., hydroxychloroquine for systemic involvement)
4. **Neoplasms:**
   - **Benign:** Surgical excision (e.g., pleomorphic adenoma)
   - **Malignant:** Surgery + radiotherapy
5. **Drug-induced Swelling:**
   - Adjust or discontinue the offending drug if possible

Pelvic Inflammatory Disease (PID)

Definition: PID is an infection of the upper female genital tract, including the uterus, fallopian tubes, and ovaries, often resulting from sexually transmitted infections (STIs).

Causes of PID

- **Infectious agents:**
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhoeae*
  - Anaerobic bacteria (e.g., *Bacteroides* species)
  - Mycoplasma genitalium
  - Post-surgical or post-procedure infections (e.g., after IUD insertion)

Risk Factors

- Multiple sexual partners
- Unprotected intercourse
- History of STIs or previous PID
- Recent intrauterine device (IUD) insertion
- Recent miscarriage, abortion, or childbirth

Clinical Features

- Lower abdominal or pelvic pain
- Fever and chills
- Abnormal vaginal discharge (often purulent)
- Dyspareunia (pain during intercourse)
- Abnormal uterine bleeding
- Cervical motion tenderness on examination (chandelier sign)

Complications

- Tubo-ovarian abscess
- Chronic pelvic pain
- Infertility (due to fallopian tube damage)
- Ectopic pregnancy
- Fitz-Hugh-Curtis syndrome (perihepatitis with right upper quadrant pain)

Diagnosis

1. **Clinical Diagnosis:**
   - Presence of pelvic pain with cervical, uterine, or adnexal tenderness
2. **Investigations:**
   - **Blood tests:** Raised CRP, ESR, leukocytosis
   - **Swabs:** Vaginal and cervical swabs for *Chlamydia* and *Gonorrhoea*
   - **Ultrasound:** To assess for tubo-ovarian abscess
   - **Laparoscopy:** Gold standard for diagnosis, used in complex or unclear cases

Management

1. **Outpatient Management:**
   - *Ceftriaxone* 500 mg IM single dose + *Doxycycline* 100 mg orally twice daily for 14 days
   - *Metronidazole* 400 mg orally twice daily for 14 days (to cover anaerobes)
2. **Inpatient Management (Severe Cases):**
   - IV *Ceftriaxone* + IV *Doxycycline*
   - Switch to oral antibiotics after clinical improvement
3. **Management of Sexual Partners:**
   - Test and treat partners for *Chlamydia* and *Gonorrhoea*
   - Abstain from intercourse until treatment is complete
4. **Surgical Intervention:**
   - Indicated in tubo-ovarian abscess rupture or failure to respond to antibiotics

Psittacosis (ornithosis)

Definition: a respiratory illness with prominent systemic manifestations caused by Chlamydia psittaci. It is transmitted to humans by inhaling organisms in dried bird feces. **Person-to-person transmission also occurs.**

Risk factors: bird exposure

Features

- Fever, pronounced headache, and dry cough with a recent history of bird exposure.
- Complications: respiratory failure, hepatitis, endocarditis, and encephalitis.

Investigations

- Chest x-ray: most often with lobar changes. 25% have multilobar changes.
- High-resolution computed tomography (HRCT): nodular pulmonary infiltrates may be surrounded by ground-glass opacities
- **Diagnostic test: serologic testing.**
- **Culture is should be avoided** (since C. psittaci is highly infectious when cultured and is only performed in specialised laboratories).

Treatment: tetracyclines are the first line. Doxycycline (100 mg orally twice daily)

> **The features of (fever, headache, myalgias, dry cough) in a patient with a history of bird contact should suggest a diagnosis of Psittacosis**

Pyrexia of Unknown Origin (PUO)

Definition: PUO is defined as a fever >38.3°C (101°F) on several occasions for at least 3 weeks, with no diagnosis after 3 days of investigation in the hospital or three outpatient visits.

Common causes

Category	Common causes
Infection (11–55%)	• Tuberculosis • Brucellosis • Q fever • Subacute bacterial endocarditis • Complicated UTI • Abscess
Inflammatory or rheumatic conditions (12–34%)	• Adult-onset Still disease • Temporal arteritis
Malignancy (7–35%)	• Hodgkin lymphoma • Non-Hodgkin lymphoma • Leukaemia • Renal cell carcinoma • Melanoma
Miscellaneous (2–20%)	• Drug fever • Cirrhosis • Postmyocardial infarction syndrome • Stroke

Diagnostic Approach

Step	Tests/Actions
History and Examination	Thorough history (travel, drug exposure, family history) and physical examination
Basic Investigations	Full blood count, CRP/ESR, blood cultures, liver function tests, urinalysis
Imaging Studies	Chest X-ray, abdominal ultrasound, CT of the chest, abdomen, and pelvis with contrast, echocardiogram
Further Testing	HIV testing, tuberculosis screening (Mantoux, Quantiferon), Rheumatoid factor, ANA, ANCA
Specialized Tests	PET scan or biopsy (if indicated based on clinical findings)

Management

1. **Empirical Treatment (when required)**
   - Empirical antibiotics only if infection is highly suspected.
   - Anti-tuberculous therapy if tuberculosis is a consideration and culture results are pending.
2. **Targeted Therapy**
   - Based on specific diagnosis from investigations (e.g., immunosuppressants for vasculitis).
3. **Supportive Care**
   - IV fluids and electrolyte management for dehydration.
   - Antipyretics (e.g., paracetamol) for fever control.

Outcome: 50% of FUO remain without an etiologic diagnosis after extensive evaluation but most of them have a good prognosis.

Q fever

Q Fever: Key Notes

Aspect	Details
Definition	Zoonotic infection caused by *Coxiella burnetii*, affecting humans and animals.
Transmission	- Inhalation of contaminated aerosols (main route) - Contact with infected animals (e.g., cattle, sheep, goats) - Rarely through unpasteurised dairy products
Incubation Period	2 to 3 weeks (varies from 5 to 40 days).
Risk Factors	- Farmers, veterinarians, and abattoir workers - Exposure to birthing animals - Inhalation of contaminated dust
Clinical Manifestations	**Acute Q Fever:** - Flu-like symptoms: fever, headache, myalgia - Atypical pneumonia - Hepatitis (elevated liver enzymes) **Chronic Q Fever:** - Endocarditis (common in patients with pre-existing valvular disease) - Vascular infections (e.g., infected aneurysms)
Diagnosis	- **Serology:** Phase I and Phase II antibodies using ELISA or indirect immunofluorescence (IFA) - **PCR:** Detects *C. burnetii* DNA (especially in early infection)
Complications	- Chronic Q fever (endocarditis, vascular infections) - Hepatitis - Neurological complications (e.g., meningoencephalitis)
Treatment	**Acute Q Fever:** - **Doxycycline 100 mg** orally twice daily for 14 days **Chronic Q Fever:** - **Doxycycline 100 mg** twice daily + **hydroxychloroquine 200 mg** three times daily for 18-24 months

Rabies

Definition: Rabies is a neurotropic, RNA rhabdovirus, transmitted by the bite of an infected animal and causes an acute encephalitis.

Incubation period of 4–12 weeks.

Transmission

- Most common animal reservoir worldwide: dogs (in the US: bats, raccoons, skunks, and foxes)
- Spread through saliva of rabid animal after bite injury

Features

- Prodrome of nonspecific flu-like symptoms, followed by acute rabies encephalitis (stupor alternating with mania and coma)
- Hydrophobia (water-provoking muscle spasms), hypersalivation
- In < 20% of cases, causes ascending flaccid paralysis → paralytic rabies
- **Atypical features** include neuropathic pain, choreiform movements of the bitten limb during the prodromal phase, focal brainstem signs, cranial nerve palsies, myoclonus, and seizures.
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

Treatment: No curative treatment, and the disease is almost always fatal.

Prevention: Following an animal bite in at risk countries: post-exposure prophylaxis (PEP)

- **If immunised:** 2 further doses of vaccine should be given
- **If not previously immunised:** human rabies immunoglobulin (HRIG) + full course of vaccination

The pathognomonic feature of rabies is hydrophobia due to pharyngeal muscle spasm. This may present along with agitation, strange behavior, mental status changes, and possibly foaming at the mouth.

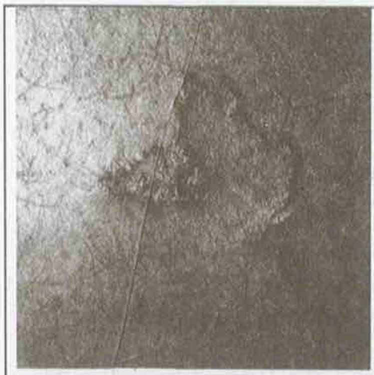
Helminths

Nematodes (roundworms)

Worm	Notes
Strongyloidiasis	**Pathogen:** *Strongyloides stercoralis* **Transmission:** Larvae are present in soil and enter the body by penetrating the skin. **Features:** ➲ GI symptoms: diarrhoea, abdominal pain/bloating ➲ papulovesicular lesions in entrance site ➲ larva currens: a linear eruption in which the larvae migrate under the skin causing pruritic, linear, urticarial rash. ➲ If the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered. **Diagnosis:** mobile larvae in stool + eosinophilia **Treatment:** Ivermectin
Enterobiasis (pinworm)	**Pathogen:** ***Enterobius vermicularis*** **Transmission:** fecal-oral **Features:** Asymptomatic in 90% of cases, perianal itching, particularly at night; girls may have vulval symptoms. **Diagnosis:** may be made by applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs **Treatment:** albendazole or mebendazole

Worm	Notes
Hookworm (ancylostomiasis, necatoriasis)	**Pathogen:** *Ancylostoma duodenale, Necator americanus* (hookworms) **Transmission:** Larvae penetrate skin of feet **Features:** Cutaneous larva migrans, GI symptoms anaemia, pulmonary symptoms (dry cough, wheeze) **Diagnosis:** eggs or worms in stool + eosinophilia **Treatment:** albendazole (400 mg once on an empty stomach)
Toxocariasis	**Pathogen:** *Toxocara canis* (dog roundworm) **Transmission:** ingestion of infective eggs. **Features:** visceral larva migrans and retinal granulomas → vision loss. **VISCious dogs → blindness. Commonest cause of visceral larva migrans** **Diagnosis:** ELISA: IgG antibodies against Toxocara + eosinophilia. **Treatment:** albendazole
Ascariasis	**Pathogen:** ***Ascaris lumbricoides*** (the most common nematode parasite of humans). Large roundworm, growing up to 35 cm in length. **Transmission:** Fecal-oral **Features:** GI symptoms + Loeffler syndrome (pneumonitis, allergy to parasite migration through the lungs, dry cough, wheeze, and eosinophil) + Intestinal or bile duct obstruction. **Diagnosis:** oval, knobby eggs in stool + Eosinophilia **Treatment:** ➲ **1st choice:** Albendazole (400 mg orally once) or mebendazole (500 mg single dose or 100 mg twice daily for 3days) ➲ **Alternative:** Ivermectin (200 mcg/kg, rounded to the nearest 3 mg dose) ➲ **In pregnancy:** Pyrantel pamoate (11 mg/kg up to a maximum of 1 g) ➲ **In bowel obstruction: Piperazine → paralyzes worms, aiding expulsion**

- **The most common cause of cutaneous larva migrans →Ancylostoma braziliense**
- **The commonest cause of visceral larva migrans → Toxocara canis**


Cutaneous larva migrans

Cutaneous larva migrans

Filariasis

Loiasis	**Pathogen:** *Loa loa* **Transmission:** by deer fly, mango fly or horse fly **Features:** red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae **Diagnosis:** blood smear + eosinophilia **Treatment:** Diethylcarbamazine
Trichinellosis	**Pathogen:** ***Trichinella spiralis*** **Transmission:** Typically develops **after eating raw** **pork**. **Features:** fever, GI symptoms, **periorbital oedema** and **myositis** (larvae encyst in muscle) **Diagnosis:** serology: IgG antibodies against Trichinella + eosinophilia **Treatment:** albendazole, or mebendazole + steroid in systemic symptoms.
***Onchocerciasis* (river blindness)**	**Pathogen:** *Onchocerca volvulus* **Transmission:** by female blackflies bite. **Features:** blindness, hyperpigmented skin and allergic reaction to microfilaria **Treatment:** Ivermectin (150 mcg/kg single dose). **rIVERblindness = IVERmectin**
Lymphatic filariasis (elephantiasis)	**Pathogen:** *Wuchereria bancrofti*, *Brugia malayi, Brugia timori.* **Transmission:** by female mosquito bite **Features:** Lymphadenopathy, LL swelling, Hydrocele **Diagnosis:** serology, blood smear. **Treatment:** ➲ 1st line: diethylcarbamazine. ➲ 2nd line: doxycycline 100 mg BID for 4 – 6 weeks ➲ In co-infection with onchocerciasis → treat onchocerciasis first, with ivermectin (150 mcg/kg single dose) alone then treat filariasis

Remember 3 L's:

1. Lymphatic filariasis (caused by Wuchereria bancrofti and Brugia malayi)
2. Loiasis (caused by Loa loa)
3. Light (light, sight, blindness - river blindness caused by Onchocerca

Tropical pulmonary eosinophilia (a clinical manifestation of lymphatic filariasis)

Mechanism: caused by an immune hyper-responsiveness to microfilariae that become trapped in the lungs.

More common in males than in females (7:1)

Features:

- dry cough that is frequently paroxysmal and nocturnal. Asthma-like attacks (breathlessness and wheezing).
- weight loss, fatigue, and malaise.

Investigations

- Blood eosinophilia, >3000/microL.
- Serum immunoglobulin E level >1000 units/mL.
- Chest radiographic → widespread ill-defined bronchocentric nodules and ground-glass infiltrates, mediastinal lymphadenopathy and pleural effusions
- The confirmatory test → ↑↑filarial antibody titers (microfilariae usually not detectable in peripheral blood)

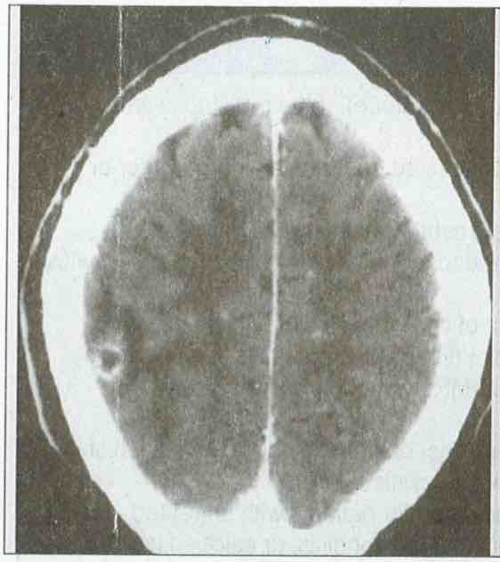
Treatment

- Diethylcarbamazine (6 mg/kg/day in three doses for 12 to 21 days)

Cestodes (tapeworms)

Disease	Notes
Hydatid disease	**Pathogen:** ***Echinococcus granulosus*** (dog tapeworm) **Transmission:** by **ingestion of eggs in dog faeces.** Dogs (definite host) ingests hydatid cysts from sheep (intermediate host). **Often seen in farmers.** **Features: liver cysts** and **anaphylaxis if cyst ruptures** (e.g. during surgical removal) **Diagnosis: ELISA testing for Echinococcus** **Treatment: Small cysts** → albendazole, or mebendazole. **Large cysts** → albendazole + surgical excision

Disease	Notes
Cysticercosis (tissue infection with tapeworm larvae e.g., muscles, brain)	**Pathogen:** larval stage (metacestode) of the pork tapeworm Taenia solium **Transmission:** eggs are ingested from contaminated water or vegetables **Features: neurocysticercosis** (can occur >30 years after infection) → seizures, headache + mass lesions in the brain 'swiss cheese appearance' **Diagnosis:** Antibody test of choice is enzyme-linked immunoelectrotransfer blot (EITB) using parasite glycoproteins performed on serum + CT/MRI with contrast (show cyst) **Treatment:** ➲ before starting antiparasitic, ophthalmologic examination should be done to exclude ocular cysticercosis. ➲ Antiparasitic is not indicated for patients with untreated hydrocephalus, cysticercal encephalitis, or calcified lesions only. ➲ For viable and/or degenerating cysts → prednisone (1 mg/kg per day) or dexamethasone (0.1 mg/kg per day) begun at least one day before antiparasitic + antiparasitic (albendazole alone if 1-2 cyst or albendazole + praziquantel if > 2 cysts) for 10 to 14 days.
Taeniasis (an intestinal infection with adult tapeworms that causes mainly GI symptoms)	**Pathogen:** *Taenia saginata (beef tapeworm) & Taenia solium (pork tapeworm)* **Transmission:** by eating undercooked beef or pork. **Features:** nausea, anorexia, or epigastric pain, and a peripheral eosinophilia. **Diagnosis:** eggs or proglottids (worm segments) in the stool **Treatment:** Praziquantel (preferred)10 mg/kg orally (single dose). Albendazole is as an alternative (400 mg orally once daily for three days) or Niclosamide four tablets (500 mg) in a single dose (2 g)



CT Finding of neurocysticercosis: Ring-enhancing lesion in the brain

CT head (with contrast; axial plane) of a patient with neurocysticercosis

A rounded peripheral lesion in the right temporoparietal region has a hypodense center and thickened enhancing wall. There is perilesional low-attenuation edema.

Trematodes (flukes)

Worm	Notes
Schistosomiasis	**Pathogen:** Schistosoma mansoni, Schistosoma haematobium and Schistosoma japonicum **Transmission:** hosted by freshwater snails (intermediate hosts), which release cercariae that penetrate skin. **Features:** 'swimmer's itch' - frequency, haematuria. **Risk factor for** squamous cell bladder cancer. **Diagnosis:** eggs in stool or urine + eosinophilia **Treatment:** Praziquantel + Corticosteroids
Paragonimisias	**Pathogen:** *Paragonimus westermani* **Transmission:** by undercooked seafood **Features:** Productive cough, hemoptysis, pleural effusions, extrapulmonary: cerebral paragonimiasis **Diagnosis:** eggs in sputum or stool + eosinophilia, ELISA + chest x-ray. **Treatment:** Praziquantel, or Triclabendazole + surgical removal of cysts
Clonorchiasis	**Pathogen: *Clonorchis sinensis*** **Transmission:** by undercooked fish **Features:** biliary tract inflammation. **Risk factor for cholangiocarcinoma** **Diagnosis:** eggs in stool + eosinophilia + ↑ alkaline phosphatase. **Treatment:** Praziquantel.

Schistosomiasis

Definition: Schistosomiasis, or bilharzia, is a parasitic flatworm infection.

Types, features and complications

S. haematobium	S. mansoni	S. japonicum
Common area: Africa and the Middle East	**Common area:** Africa and South America	**Common area:** East Asia
Features: Haematuria, dysuria	**Features:** diarrhoea, abdominal pain	
Local complications (chronic infection) • Squamous cell carcinoma of the bladder • Bladder neck obstruction and hydronephrosis	**Local complications (chronic infection):** • Intestinal bleeding, bowel stricture • periportal fibrosis, portal hypertension and splenomegaly.	
Systemic complications: • **Pulmonary schistosomiasis** (pulmonary hypertension and cor pulmonale) • **Nephrotic syndrome.** • **Neuroschistosomiasis** ⇨ Spinal (more common than cerebral) → transverse myelitis. ⇨ Cerebral: epilepsy		

- **Acute schistosomiasis syndrome (Katayama fever):** develops 3-8 weeks after initial infection include a serum sickness-like reaction (e.g., fever, rash, myalgias), cough, diarrhea, abdominal pain, and eosinophilia and is self-limited.
- **Chronic infection:** characterized by **chronic granulomatous inflammation** in response to the deposition of eggs of the Schistosoma. Can affect the gastrointestinal, pulmonary, genitourinary, and central nervous systems.
- **Neuroschistosomiasis:** transverse myelitis , seizure. ***S. japonicum*** is the commonest cause of *Schistosoma* encephalitis (due to smaller eggs) whereas *S. masoni and S. haematobium tend to affect spinal cord* (larger eggs → difficult to reach the brain).

Management

- **Acute schistosomiasis syndrome (Katayama fever):** corticosteroids (to reduce inflammation, because praziquantel may aggravate symptoms within the 12 weeks of infection) + praziquantel 8 to 12 weeks after infection (together with prednisolone), followed by repeat praziquantel treatment 4 to 6 weeks later (without corticosteroids)
- **Chronic infection:** praziquantel (single dose): 40 mg/kg for S.haematobium, S.mansoni, or S.intercalatum and 60 mg/kg for S.japonicum or S. mekongi.
- **CNS involvement (neuroschistosomiasis): prednisolone 1 mg/kg per day (started immediately) and Praziquantel (started a few days after initiation of steroid)**

Trypanosomiasis

Two main form of this protozoal disease are recognised: African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

African trypanosomiasis (sleeping sickness)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen:

	West African sleeping sickness (Gambian trypanosomiasis)	East African sleeping sickness (Rhodesian trypanosomiasis)
Pathogen	Trypanosoma brucei gambiense	Trypanosoma brucei rhodesiense
Vector	Tsetse fly	
	Glossina palpalis	Glossina morsitans
Regions	Central and West Africa	Eastern and southeastern Africa
Primary reservoir	Humans	Cattle, antelope
Clinical course	• Chronic, slowly progressive disease • Trypanosomal chancre is less common • Low parasitemia • Lower risk of myocarditis • Trypanids are less common • Prominent lymphadenopathy • Late CNS manifestations	• Acute disease with poor demarcation between stages • Trypanosomal chancre is more common. • High parasitemia • Higher risk of myocarditis • Trypanids are more common • Mild lymphadenopathy • Early CNS manifestations

- **Features**
  - ⇨ **First stage** (haematolymphatic spread)
    - Trypanosoma chancre - painless subcutaneous nodule at site of infection
    - Intermittent fever and erythematous, or maculopapular rash
    - Lymphadenopathy (discrete, rubbery, non-tender nodes) and mild hepatosplenomegaly.
  - ⇨ **Second stage**: meningoencephalitic stage (occurs months or years after infection)
    - Behavioral changes: confusion, apathy, psychosis.
    - Reversal of the sleep wake (daytime somnolence with night-time insomnia)
    - Extrapyramidal signs and ataxia.
- **Management**
  - ⇨ **Early disease:** IV pentamidine or **suramin**
  - ⇨ **Later disease or CNS involvement: IV melarsoprol**

American trypanosomiasis, (Chagas' disease)

- **Caused by** the protozoan ***Trypanosoma cruzi.***
- **Transmitted by** triatomine bug bite.

- **Features:**
  - ⇨ **Acute phase:**
    - asymptomatic (95%)
    - chagoma (an erythematous nodule at site of infection)
    - periorbital oedema
  - ⇨ **Chronic Chagas' disease**
    - **Cardiac feature:** myocarditis may lead to dilated cardiomyopathy and arrhythmias **(the common cause of death)**
    - **GIT feature:** Mega-oesophagus (causing dysphagia) and Mega-colon (causing constipation)
    - **CNS feature:** meningoencephalitis
- **Management**
  - ⇨ Acute phase: azole or **benznidazole** or nifurtimox
  - ⇨ Chronic disease: treating the complications e.g., heart failure.

Rickettsial infections

Definition: Rickettsia is a weakly gram-negative intracellular bacteria, that primarily infects vascular endothelial cells causing systemic vasculitis

Diseases	Pathogen	Reservoir	Characteristics	Diagnosis	Antibiotic of choice
Rocky Mountain spotted fever	**Rickettsia rickettsii**	Arthropods (dog ticks)	Fever Rash (**rash on the palms and soles is highly characteristic**) complications: encephalitis, noncardiogenic pulmonary edema (ARDS), arrhythmias, coagulopathy, GI bleeding.	PCR	➲ Doxycycline ➲ Chloramphenicol (pregnant patients)
Epidemic typhus	**Rickettsia prowazekii**	Human to human (body louse)	Fever and rash maculopapular rash **that classically begins centrally, and spreads outwardly sparing the palms and soles**	Serologic tests	
Endemic (murine) typhus	**Rickettsia typhi**	Arthropods (fleas)			

Histoplasmosis

Overview

Aspect	Details
Definition	Fungal infection caused by *Histoplasma capsulatum*, typically found in soil enriched with bird or bat droppings.
Epidemiology	Common in areas such as the Ohio and Mississippi River Valleys in the USA; can affect immunocompromised individuals (e.g., HIV/AIDS).
Transmission	Inhalation of airborne spores from contaminated soil, bird, or bat droppings.
Incubation Period	3–17 days after exposure.

Clinical Manifestations

Form	Features
Asymptomatic Infection	Most common form; usually self-limiting without symptoms.
Acute Pulmonary Histoplasmosis	Fever, cough, chest pain, fatigue, and shortness of breath.
Chronic Pulmonary Histoplasmosis	Resembles tuberculosis; progressive lung infiltrates, weight loss, and night sweats.
Disseminated Histoplasmosis	Affects multiple organs (e.g., liver, spleen); common in immunocompromised patients with symptoms like fever, hepatosplenomegaly, and weight loss.
Cutaneous Lesions	Rare, but may occur in disseminated disease.

Complications

- Pulmonary fibrosis
- Mediastinal granulomas
- Adrenal insufficiency (in disseminated disease)
- Meningitis or encephalitis in CNS involvement

Diagnosis and Findings

Investigation	Findings
Histoplasma antigen test	Detects antigens in urine or serum (especially useful in disseminated cases).
Serology	Detection of antibodies (less sensitive in acute infections).
Culture	Growth of *Histoplasma capsulatum* from clinical samples (e.g., sputum, blood); takes several weeks.
Histopathology	Granulomas and yeast forms visible on biopsy.
Chest X-ray/CT	Pulmonary infiltrates, mediastinal lymphadenopathy, and nodules.

Management

Form	Treatment
Mild to moderate acute pulmonary histoplasmosis	Itraconazole 200 mg orally 2–3 times daily for 6–12 weeks.
Severe acute or disseminated histoplasmosis	Amphotericin B (liposomal) 3–5 mg/kg IV daily for 1–2 weeks, followed by Itraconazole for 12 months.
Chronic pulmonary histoplasmosis	Itraconazole 200 mg orally 2–3 times daily for 12–24 months.
CNS involvement	Amphotericin B initially, followed by Itraconazole for 12 months.
HIV/AIDS-related histoplasmosis	Lifelong suppressive therapy with Itraconazole 200 mg daily if CD4 < 150 cells/μL.

Differential diagnosis: sarcoidosis, tuberculosis, and malignancy.

> **Histoplasmosis must be excluded before treating patients with presumed sarcoidosis with immunosuppressive medications.**

NOTES & NOTES

4TH Edition

VOL 4

2025-2026

DR. YOUSIF ABDULLAH HAMAD
MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

FBC
Fareed Book Centre

© Copyright 2025-2026

NOTES AND NOTES

4th Edition

DR. YOUSIF ABDULLAH HAMAD
MRCP (GLASGO-UK), MRCP - IRELAND

for MRCP, Part 1 & 2

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the Copyright Holders.

This book is sold subject to the condition that it shall not, by way of trade or otherwise, be lent, resold, hired out or otherwise circulated without the publisher's prior consent in any form of binding or cover other than that in which it is published and without a similar condition including this condition being imposed on the subsequent purchaser.

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editors, contributors and the publishers have, as far as it is possible, taken care to ensure that the information given in this text is accurate and up-to-date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice. Neither the publisher nor the authors assume any responsibility for any loss or injury and/or damage to person or property arising out of or related to any use of the material contained in this handbook.

Copyright © 2025-2026 All Rights Reserved

FBC Fareed Book Centre
Fareed Book Centre
Discover Something New
www.fareedbookcentre.com
156/8, MCB Road, Gulgasht Multan. | 03081401299

SOLE DISTRIBUTOR

Head Office 156/B (Fareed Book Centre) Gulgasht Colony Multan
03081401299
Info@fareedbookcentre.com

Shop No. 9 adjacent Bakhtawar Amir Medical & Dental College Multan
03168081199
Info@fareedbookcentre.com

V-4

Contents

SL	Topic	Page
	Ophthalmology	1
1	Acute angle closure glaucoma (AACG)	2
2	Primary open-angle glaucoma (POAG)	3
3	Age related macular degeneration (AMD)	5
4	Cataracts	7
5	Angioid retinal streaks	9
6	Mydriasis	10
7	Optic Atrophy	12
8	Optic Neuritis	13
9	Relative Afferent Pupillary Defect (RAPD)	15
10	Herpes zoster ophthalmicus	17
11	Keratitis	18
12	Red eye	21
13	Anterior Uveitis	22
14	Episcleritis	23
15	Subconjunctival Haemorrhage	24
16	Posterior Uveitis	25
17	Retinitis	26
18	Retinitis Pigmentosa (RP)	27
19	Sudden painless loss of vision	29
20	Amaurosis Fugax	30
21	Tunnel Vision	32
22	Hyphaema	33
	Dermatology	35
23	Skin Layers	36
24	Descriptive Terms for Skin Lesions	36
25	Acanthosis Nigricans	37
26	Acne Rosacea	38
27	Acne Vulgaris	38
28	Isotretinoin	40
29	Alopecia	41
30	Alopecia Areata	41
31	Pemphigus Vulgaris	42
32	Bullous Pemphigoid	43
33	Dermatitis Herpetiformis (DH)	45
34	Discoid Lupus Erythematous	46
35	Contact Dermatitis	48
36	Pruritus	49
37	Eczema Herpeticum	49
38	Eczema: Topical Steroids	50
39	Pompholyx	51
40	Erythema Ab Igne	51
41	Erythema Multiforme	52
42	Stevens-Johnson Syndrome (SJS) And Toxic Epidermal Necrolysis (TEN)	55
43	Erythema Nodosum (EN)	57
44	Erythema Induratum (EI)	58
45	Erythrasma	59
46	Erythroderma	59
47	Onycholysis	60
48	Fungal Nail Infections (Onychomycosis)	61
49	Granuloma Annulare	62
50	Herpes Simplex Virus (HSV) And Skin Disorders	63
51	Molluscum Contagiosum	63
52	Impetigo	64
53	Erysipelas	65
54	Lichen Planus	66
55	Lichen Sclerosus	68
56	Lichen Simplex Chronicus (LSC)	68
57	Lichen Amyloidosis	69
58	Pityriasis Rosea	70
59	Pityriasis Versicolor	70
60	Psoriasis	71
61	Pyoderma Gangrenosum	75
62	Scabies	76
63	Seborrhoeic Dermatitis	77
64	Skin Disorder In Pregnancy	79
65	Lupus Vulgaris	80
66	Spider Nevi	81

67	Tinea	82
68	Vitiligo	84
69	Angular Stomatitis	85
70	Venous Ulceration	86
71	Pressure Ulcers	87
72	Keloid Scars	88
73	Increased Skin Fragility	88
74	Livedo Reticularis (LR)	89
75	Hyperhidrosis	90
76	Basal Cell Carcinoma (BCC)	90
77	Squamous Cell Carcinoma (SCC)	92
78	Keratoacanthoma (KA)	93
79	Malignant Melanoma	94
80	Moles (Melanocytic Nevi)	95
81	Angiosarcoma	96
82	Pyogenic Granuloma	97
83	Skin Disorders Associated With Malignancy	98
84	Keratosis	99
	Psychiatry	101
85	Unexplained Symptoms	102
86	Eating disorders	103
87	Antipsychotics	106
88	Typical Antipsychotics	107
89	Atypical Antipsychotics	107
90	**Comparison**: Neuroleptic Malignant Syndrome (NMS) vs. Serotonin Syndrome (SS)	109
91	Typical Antidepressants	110
92	Selective Serotonin Reuptake Inhibitors (SSRIs)	111
93	Selective Serotonin-Norepinephrine Reuptake Inhibitors (SSNRIs)	112
94	Tricyclic Antidepressants (TCAs)	113
95	Atypical antidepressants	114
96	Benzodiazepines	115
97	Post-Traumatic Stress Disorder (PTSD)	117
98	Grief Reaction	118
99	Depression	119
100	Generalised Anxiety Disorder (GAD)	122
101	Hyperventilation Syndrome (HVS)	123
102	Cognitive Behavioural Therapy (CBT)	124
103	Body Dysmorphic Disorder (BDD)	126
104	Post-Partum Mental Health Problems	127
105	**Alcohol - Problem Drinking**: Management	128
106	Alcohol Withdrawal	129
107	Psychosis	131
108	Schizophrenia	132
109	Electroconvulsive Therapy (ECT)	134
110	Personality Disorders	135
111	Panic Disorder	136
112	Acute Confusional State (Delirium)	137
113	Delusions	138
114	Hallucination	139
115	Charles Bonnet Syndrome (CBS)	140
116	Hypnogogic and Hypnopompic Hallucinations	141

Pharmacology

SL	Topic	Page
	Pharmacology	143
1	Basic Pharmacology	144
2	Drug Absorption	146
3	Lipid Soluble Drug vs Lipid Insoluble Drug	148
4	Lipophilic, Hydrophilic and Amphiphilic	149
5	First-Order Kinetics vs Zero-Order Kinetics	149
6	Prodrugs	151
7	Clinical Trial: Phases	152
8	P450 Enzyme System	152
9	Therapeutic Drug Monitoring (TDM)	154
10	Drug Causes Gingival Hyperplasia	156
11	Drug Causes SIADH	157
12	Drug-Induced Impaired Glucose Tolerance	158
13	Drug-Induced Pancytopaenia	159
14	Drugs Causing Ocular Problems	160
15	Drug Induced Seizures	161
16	Drugs Acting on Serotonin (5-HT) Receptors	162
17	Antibiotics: General overlook	163
18	Tetracyclines	167
19	Macrolides	168
20	Fluoroquinolones	169
21	Aminoglycosides	170
22	Cotrimoxazole: Trimethoprim-Sulfamethoxazole (TMP/SMX)	171
23	Beta-lactams Antibiotics	172
24	Vancomycin	174
25	Linezolid	175
26	Antiviral Agents	176
27	Anti-Fungal	177
28	**Overdose and Poisoning:** Management	178
29	Toxic Alcohol Poisoning	180
30	Ecstasy (MDMA) Poisoning	181
31	Opioid Toxicity	182
32	Lead Poisoning	184
33	Paracetamol Overdose	185
34	Salicylate Overdose	188
35	Organophosphate Insecticide Poisoning	189
36	Antihistamines	190

Basic Science

SL	Topic	Page
	Basic Science	193
	Immunology	194
1	Immune System Response	194
2	Cells of the Immune System	195
3	Cytokines and Interleukins	196
4	Human Leukocyte Antigen (HLA)	198
5	Cluster of Differentiation (CD Markers)	200
6	Immunoglobulins (Antibodies)	201
7	Complement System	202
8	Autoimmune Diseases and Autoantibodies	204
9	Primary immunodeficiency	206
10	Selective IgA Deficiency	208
11	IgG Subclass Deficiency	209
12	Common Variable Immunodeficiency (CVID)	210
13	Bruton's Agammaglobulinemia (X-linked Agammaglobulinemia)	211
14	Severe Combined Immunodeficiency Disease (SCID)	212
15	DiGeorge Syndrome	212
16	Wiskott-Aldrich Syndrome (WAS)	213
17	Complement Deficiencies	214
18	Hereditary Angioedema	216
19	Hypersensitivity	217
20	Anaphylaxis	218
21	Exercised Induced Anaphylaxis	221
22	Anaphylactic Reactions Associated with Anaesthesia	222
23	Allergy Tests	223
24	Latex Allergy	224
25	Serum Sickness	225

	Biochemistry & Metabolism	227
1	Anion gap (AG)	228
2	Metabolic Alkalosis	229
3	Respiratory Acidosis	231
4	Respiratory Alkalosis	232
5	Hyperkalaemia	233
6	Pseudohyperkalaemia	236
7	Hypokalaemia and Acid-Base Balance	237
8	Hypernatraemia	239
9	Hyponatraemia	240
10	Hypomagnesaemia	244
11	Hypermagnesaemia	246
12	Hypophosphataemia	247
13	Hyperphosphataemia	248
14	Vitamin B3 (Niacin) Deficiency	249
15	Vitamin C Deficiency (Scurvy)	250
16	Vitamin B12 Deficiency	251
17	Vitamin B1 (Thiamine) Deficiency	253
18	Vitamin E Deficiency	254
19	Vitamin K Deficiency	254
20	Vitamin A Deficiency	255
21	Vitamin and Selenium Deficiency	256
22	Zinc Deficiency	257
23	Pyruvate Kinase	258
	Genetics	259
1	Autosomal Dominant Conditions	260
2	Achondroplasia	262
3	Osteogenesis Imperfecta ("Brittle Bone Disease")	263
4	Down's Syndrome	264
5	Noonan's Syndrome	267
6	Autosomal Recessive Conditions	268
7	Ehlers–Danlos Syndrome (EDS)	269

8	Pseudoxanthoma Elasticum (PXE)	271
9	Phenylketonuria (PKU)	272
10	Alkaptonuria	273
11	X-linked Recessive	274
12	X-linked Dominant Disorders	276
13	Mitochondrial Diseases	277
14	Kearns-Sayre Syndrome	278
15	Kallman's Syndrome	279
16	Klinefelter's Syndrome	281
17	Turner's Syndrome	282
18	Marfan's Syndrome	284
19	Homocystinuria	285
20	Fragile X Syndrome	287
21	Trinucleotide Repeat Disorders	287
22	Polygenic Diseases	288
23	Gaucher's Disease	289
24	Fabry's Disease	291
25	Mucopolysaccharidoses (MPS)	292
26	Glycogen Storage Disorders (GSD)	293
27	Collagen Types	296
28	McArdle's Disease	298
29	Linkage Disequilibrium	299
30	Prader-Willi Syndrome	300
31	Mutations	301
32	Chromosome Abnormality	302

33	McCune–Albright Syndrome (MAS)	303
	Biostatistics & EBM	305
1	Hypothesis	306
2	P-Value	308
3	Choosing the Appropriate Statistical Test	309
4	Distribution	313
5	Standard Deviation	316
6	Confidence Interval (CI) and Standard Error of the Mean (SEM)	317
7	Screening test Statistics	319
8	Incidence and Prevalence	326
9	Scales of Measurement	327
10	Overview of Study designs	328
11	Cross-Sectional Study	331
12	Randomised Controlled Trial (RCT)	332
13	Cohort Study	333
14	Case-Control Study	334
15	Systematic Review and Meta-Analysis	335
16	Common Biases in Studies	336
17	Types of Trials	338
18	Study Design: Evidence and Recommendations	339
19	Study Design for New Drug Evaluation	340

4th edition 2025

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Chapter- 10

Minors

Ophthalmology
Dermatology
Psychiatry

OPHTHALMOLOGY

Acute angle closure glaucoma (AACG)

Definition

- sudden and sharp **increase in intraocular pressure (IOP)** caused by an obstruction of aqueous outflow (most commonly as a result of an occlusion of the iridocorneal angle)

Pathophysiology:

- blockage of the trabecular meshwork → ↓ drainage of aqueous humor from the eye → ↑ IOP

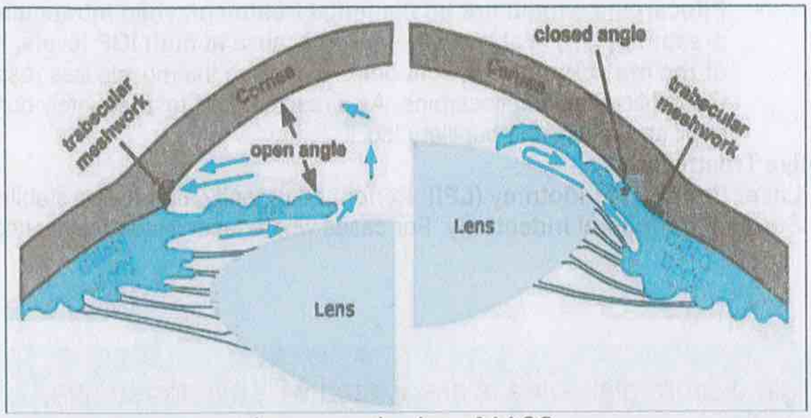


Image: mechanism of AACG

Risk factors

- hypermetropia (long-sightedness)
- lens growth associated with age
- neovascular glaucoma (new blood vessels grow into the angle of the eye and block the aqueous outflow). Vascular endothelial growth factor (VEGF) is a growth factor protein that works by stimulating angiogenesis. Hence, inhibiting VEGF (e.g. Bevacizumab) can stop the progression of neovascularization.
- **Drugs:** pupillary dilatation by mydriatic drops, **anticholinergics (e.g., atropine) and tricyclic antidepressants**

Features

- Sudden onset of symptoms
- Unilaterally inflamed, reddened, and severely painful eye (hard on palpation)
- Blurred vision and halos seen around light
- Mid-dilated, irregular, unresponsive pupil
- Frontal headaches, vomiting, nausea
- Complications: rapid permanent vision loss due to ischemia and atrophy of the optic nerve symptoms worse with mydriasis (e.g. watching TV in a dark room)

Diagnosis

- **Tonometry:** → Elevated IOP (> 21 mm Hg). AACG: Often >40 mmHg.
- **Gonioscopy: the gold-standard diagnostic test** → Narrowing/closure of the iridocorneal angle.

Management

- Urgent referral to an ophthalmologist
- **Rapid IOP Reduction (Pharmacological Therapy)**
  - **Topical Beta-blocker (e.g., Timolol 0.5%)**: 1 drop every 12 hours.
  - **Topical Alpha-agonist (e.g., Apraclonidine 1%)**: 1 drop every 12 hours.
  - **Systemic Carbonic Anhydrase Inhibitor (e.g., Acetazolamide 500 mg IV/PO)**: IV is preferred in severe cases for faster action.
  - **Osmotic Agent (e.g., Mannitol IV, 1-2 g/kg)**: **Use in cases of refractory high IOP.**
  - **Topical Miotic (e.g., Pilocarpine 1-2%)**: Initiate once the IOP starts decreasing to induce miosis and reopen the angle.
    - **Pilocarpine should not be the initial treatment when intraocular pressure (IOP) is above 40 mmHg** because **at high IOP levels, ischemia of the iris sphincter muscle occurs**, making the muscle less responsive to the miotic effect of pilocarpine. As a result, it fails to adequately constrict the pupil and relieve the pupillary block.
- **Definitive Treatment**
  - **Laser Peripheral Iridotomy (LPI)**: Performed urgently after IOP is stabilised.
  - **Surgical Peripheral Iridectomy**: For cases where laser is contraindicated or fails.

Top Tips

Acute angle closure glaucoma is associated with hypermetropia, where as primary open-angle glaucoma is associated with myopia

Treatment of acute glaucoma - acetazolamide + pilocarpine

Do not use mydriatic drugs (e.g., atropine and epinephrine) during ophthalmologic examination in patients with acute angle-closure glaucoma! Moreover, do not cover the eye, since darkness induces mydriasis and worsens the condition

Primary open-angle glaucoma (POAG)

Epidemiology

- **The most common type of glaucoma.** present in 2% of people older than 40 years.
- Second leading cause of blindness following age-related macular degeneration (AMD).

Pathophysiology

- Impaired aqueous humor drainage through the trabecular meshwork, leading to increased IOP.
- Mechanical and vascular damage to the optic nerve head (glaucomatous cupping).
- Progressive loss of retinal ganglion cells and axons, resulting in visual field defects.

Risk factors

- age, family history, black patients, myopia, hypertension, diabetes mellitus

Features

- **bilateral, progressive visual field loss (from peripheral to central) (Loss of nasal visual field) progressing to 'tunnel vision'**
- Fundoscopy: cupping and pallor of optic disc

Diagnosis

- Intraocular Pressure Measurement (Tonometry):
  - Normal range: 10–21 mmHg.
  - Elevated IOP in POAG (but normal-pressure glaucoma is also possible).
- **Fundoscopy: Optic nerve head changes**:
  - Increased cup-to-disc ratio.
  - Thinning of the neuroretinal rim.
  - Disc hemorrhages (in some cases).
- Visual Field Testing (Perimetry):
  - Detects characteristic **glaucomatous field defects**.
  - Useful for monitoring disease progression.
- Gonioscopy: Confirms **open anterior chamber angle**, ruling out angle-closure glaucoma.
- Optical Coherence Tomography (OCT):
  - Measures **retinal nerve fiber layer (RNFL)** thickness.
  - Detects early optic nerve damage.

Management: Goals → Lower IOP to slow or prevent progression of optic nerve damage.

- **Pharmacological Therapy:**
  - **Prostaglandin analogues (e.g., Latanoprost 0.005%)**:
    - *Mechanism*: Increases uveoscleral outflow.
    - *Side effects*: Iris pigmentation, eyelash growth.
  - **Beta-blockers (e.g., Timolol 0.5%)**:
    - *Mechanism*: Reduces aqueous humor production.
    - *Side effects*: Bradycardia, hypotension.
  - **Alpha-agonists (e.g., Brimonidine 0.2%)**:
    - *Mechanism*: Reduces production and increases outflow.
  - **Carbonic anhydrase inhibitors (e.g., Dorzolamide 2%)**:
    - *Mechanism*: Reduces aqueous humor production.
    - *Side effects*: Ocular discomfort, bitter taste.
  - **Rho kinase inhibitors (e.g., Netarsudil)**:
    - *Mechanism: Increases trabecular outflow.*
    - *Side effects*: Conjunctival hyperemia.
- **Laser Therapy: Laser Trabeculoplasty**:
  - Improves trabecular outflow.
  - Indicated when medications are insufficient.
- **Surgical Options:**
  - **Trabeculectomy**: Creates a fistula for aqueous humor drainage.
  - **Drainage implants**: Used in refractory cases.
  - **Minimally invasive glaucoma surgery (MIGS)**: Safer option in mild-to-moderate cases.

Medications for Primary Open-Angle Glaucoma

Medication	Mode of Action	Notes
Prostaglandin analogues (e.g., Latanoprost)	Increases uveoscleral outflow	- Once daily administration. - **Preferred first-line therapy.** - **Suitable for patients with asthma.** **Adverse effects:** - Brown pigmentation of the iris. - Growth of eyelashes. - Epithelial keratopathy. - **Systemic:** Paresthesia, hypokalemia, renal stones, acidosis, aplastic anemia.
Beta-blockers (e.g., Timolol)	Reduces aqueous production	- **Avoid in asthmatics and patients with heart block.**
Sympathomimetics (e.g., Brimonidine)	Reduces aqueous production and increases outflow	- Avoid if taking MAOIs or tricyclic antidepressants. **Adverse effects:** Hyperaemia.
Carbonic anhydrase inhibitors (e.g., Acetazolamide)	Reduces aqueous production	- Systemic absorption may cause sulphonamide-like reactions.
Miotics (e.g., Pilocarpine)	Increases uveoscleral outflow	**Adverse effects:** Constricted pupil, headache, and blurred vision.

Age related macular degeneration (AMD)

Epidemiology

- The most common cause of blindness

Pathophysiology

- progressive degenerative changes in the **central part** of the retina (macula) → visual impairment

Risk factors:

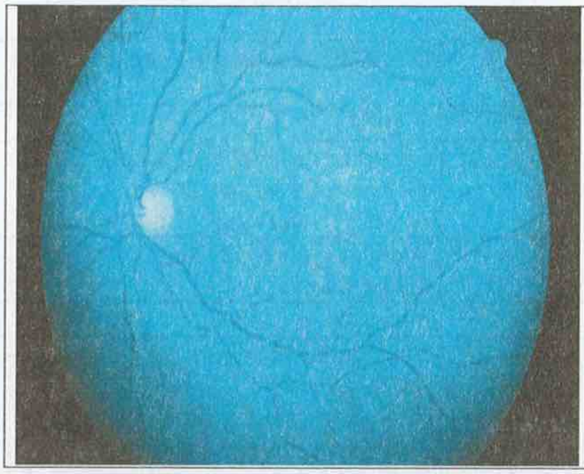
- Advanced age, smoking

Classification

	Dry AMD (nonexudative, atrophic)	Wet AMD (exudative , neovascular)
Prevalence	~ 90%	~ 10%
Pathophysiology	Deposition of drusen (yellow round spots) in the retinal pigment epithelium.	Choroidal neovascularization (between the retinal pigment epithelium and Bruch's membrane)
Onset	slow progressive visual impairment (**usually over decades**)	acute or insidious onset (over weeks to months)
Presentation	Bilateral	manifests in one eye
Fundoscopy	Drusen **(a small, yellowish, granular, subretinal deposits that are age related).**	Subretinal and intraretinal hemorrhage and/or exudate. **if neovascularisation is present fluorescein angiography is performed**
Treatment	Supportive: stop smoking Diet: high dose of beta-carotene, vitamins C and E, and zinc. **Supplements should be avoided in smokers due to an increased risk of lung cancer**	First-line: injection of VEGF inhibitors (ranibizumab, bevacizumab, pegaptanib) into the vitreous body.
Symptoms	Reduced visual acuity: 'blurred', 'distorted' vision, **central vision is affected first** (**central scotomas**)	

Differential diagnosis

Differential diagnosis of vision loss		
Condition	**Clinical features**	**Fundoscopy**
Age related macular degeneration	• May be insidious (dry AMD) or rapid (wet AMD) onset • Impairment of central vision only (vision loss is rare)	• Drusen • Macula depigmentation
Open-angle glaucoma	• Insidious onset • Peripheral vision loss (tunnel vision)	• Disc cupping with high intraocular pressure
Central Vessel occlusion (retinal artery)	• Acute or subacute onset • Complete vision loss	• Swollen disc • Retinal haemorrhages • Cotton wool spots
Retinal detachment	• Acute onset • Partial or complete vision loss (falling curtain)	• Detached or floating retina
Cataract	• Insidious onset • Blurred, dim vision, and a glare • Absent or opacified red-reflex	• Retina may not be visible (in advanced disease)



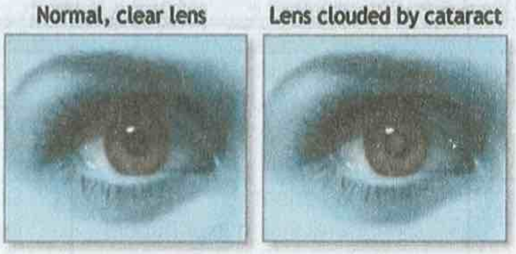
The fundus shows small pale dots over the macular area typical of drusen.
This is macular degeneration and one of the commonest causes of blindness.

Top tips

Drusen = Dry macular degeneration

Macular degeneration - smoking is risk factor

Cataracts



A cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity

Definition

- opacification of the lens

Causes

- **Majority**
  - ⇨ age related (Senile cataracts)
    - the most common cause
      - ❖ 17% of people older than 40 years
      - ❖ 50% of people older than 75 years
  - ⇨ UV light

- **Systemic**
  - ⇨ diabetes mellitus
  - ⇨ steroids
    - **Inhaled steroids can cause cataracts**
  - ⇨ infection (congenital rubella)
  - ⇨ metabolic:
    - diabetes
    - hypocalcaemia,
    - galactosaemia
      - ❖ but if the galactosaemia is treated, the cataract is reversible.
  - ⇨ myotonic dystrophy,
  - ⇨ Down's syndrome
- **Ocular**
  - ⇨ trauma
  - ⇨ uveitis
  - ⇨ high myopia
  - ⇨ topical steroids

Feature

- Symptoms
  - ⇨ painless, progressive, and slow vision loss
- Physical exam
  - ⇨ absent red reflex

Classification

- **Nuclear sclerosis**:
  - ⇨ **the most common type** of cataract,
  - ⇨ involves the central or 'nuclear' part of the lens.
  - ⇨ **common in old age**
  - ⇨ reduction of vision is the major symptom.
  - ⇨ change lens refractive index,
    - often leads to an **increase in refractive power of the lens** causing **nearsightedness (problems with distance vision)**.
- **Polar:** localized, commonly inherited, lie in the visual axis
- **Subcapsular:**
  - ⇨ glare is the major symptom
    - **Glare** is difficulty seeing in the presence of bright light such as direct or reflected sunlight or artificial light such as car headlamps at night.
  - ⇨ due to steroid use, just deep to the lens capsule, in the visual axis
  - ⇨ **Posterior subcapsular cataracts** are associated with:
    - **retinitis pigmentosa**
    - **chronic steroid** use.
  - ⇨ Anterior subcapsular cataracts are associated with:
    - idiopathic or
    - secondary to trauma and iotragenic causes.
- **Dot opacities**
  - ⇨ common in normal lenses,
  - ⇨ also seen in:
    - diabetes
    - myotonic dystrophy

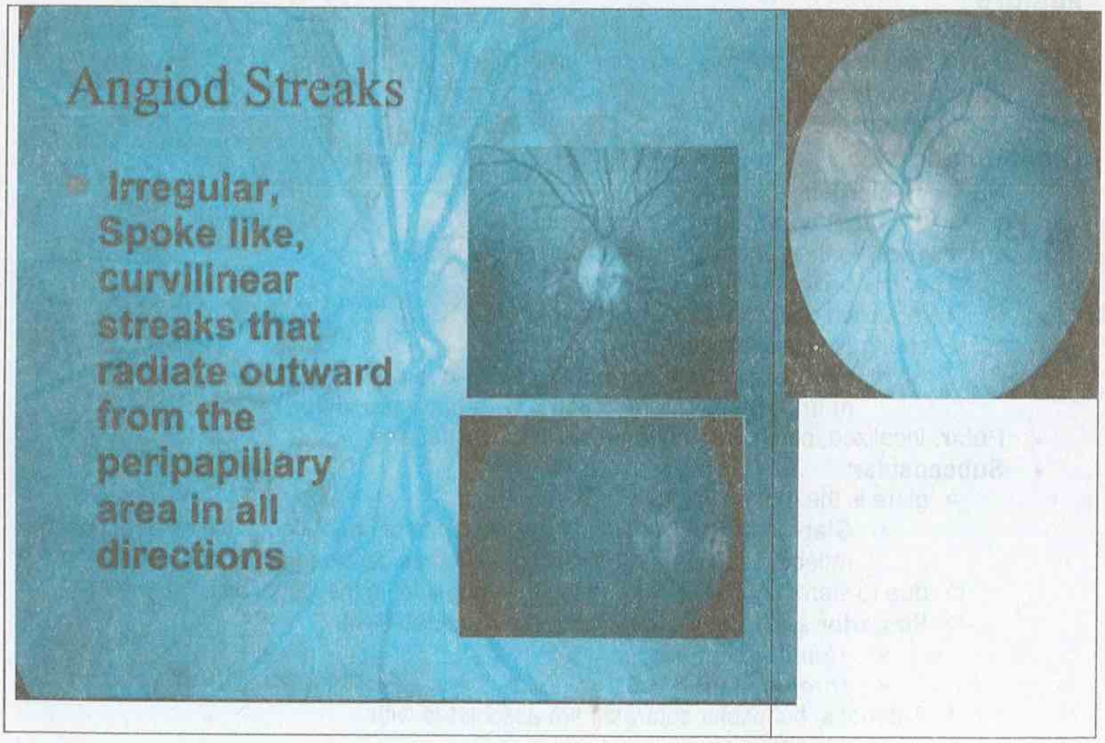
Angioid retinal streaks

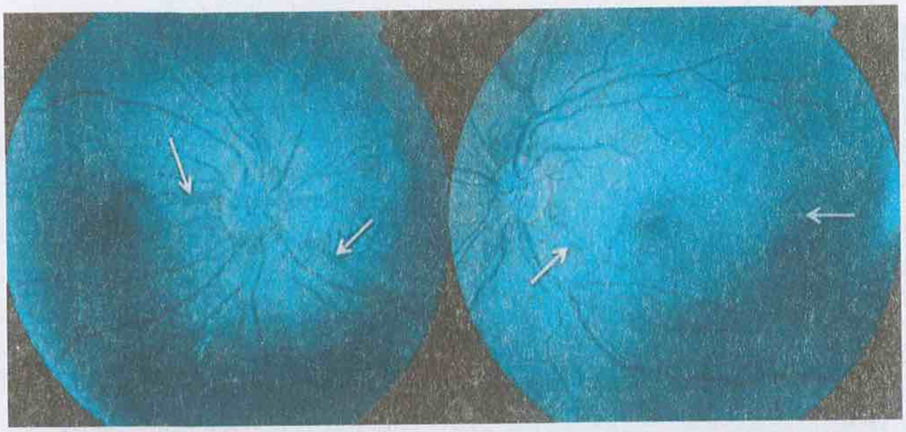
Definition

- Angioid retinal streaks are seen on fundoscopy as irregular dark red streaks radiating from the optic nerve head. They are caused by degeneration, calcification and breaks in Bruch's membrane .

Causes: A useful mnemonic for angioid retinal streak is **SLAPPERS**:

- S - **Sickle-cell anaemia**
- L - Lead poisoning
- A - Abetalipoproteinaemia/acromegaly
- P - **Paget's disease** /phacomatoses (tuberous, sclerosis, neurofibromatosis, Sturge-Weber)
- P - **Pseudoxanthoma elasticum**
- E - Ehlers-Danlos syndrome
- R - Raised calcium or phosphate
- S - Short people (dwarfism).





Mydriasis

Causes of mydriasis (large pupil)

- third nerve palsy
- Holmes-Adie pupil
- traumatic iridoplegia
- phaeochromocytoma
- congenital
- **Drug causes of mydriasis**
  - ⇨ topical mydriatics: tropicamide, atropine
  - ⇨ sympathomimetic drugs: amphetamines, pseudoephedrine, amphetamines and **cocaine,**
  - ⇨ anticholinergic drugs: eg antihistamines, atropine and tricyclic antidepressants
  - ⇨ Poisons (atropine, CO, ethylene glycol).

Miosis

Causes of small pupils include:

- Horner's syndrome
- Old age
- **Pontine haemorrhage**
- Argyll Robertson pupil
- Drugs, and
- Poisons (opiates, organophosphates).

Anisocoria, Holmes-Adie Pupil, and Argyll Robertson Pupil

Condition	Definition/Key Features	Causes/Notes
Anisocoria	Unequal pupil sizes. Difference >0.4 mm in dim or bright light.	- Can be physiological (benign, ~20% of population). - Pathological causes include: - Horner's syndrome (sympathetic defect). - Oculomotor nerve palsy (parasympathetic defect). - Mechanical trauma or iris abnormalities.
Holmes-Adie Pupil	Unilateral dilated pupil with delayed constriction to light and near accommodation.	- Caused by a lesion in the ciliary ganglion or postganglionic fibres. - Often associated with diminished deep tendon reflexes (Holmes-Adie syndrome). - More common in young women.
Argyll Robertson Pupil	Bilaterally small pupils that accommodate but do not constrict to light ("light-near dissociation").	- Associated with **neurosyphilis** (classic cause) and rarely diabetic neuropathy. - Pupils are irregular in shape and do not dilate well in darkness. - "Prostitutes' pupils" (accommodate but don't react).

Holmes ADIe = DIlated pupil, females, absent leg reflexes

Abnormally dilated pupil (mydriasis) which does not constrict in response to light, loss of deep tendon reflexes, and abnormalities of sweating.

The history of anisocoria, with headaches and diplopia should ring alarm bells, in that a life-threatening posterior communicating artery aneurysm/berry aneurysm needs to be excluded urgently.

Optic Atrophy

Definition

- Optic atrophy refers to the degeneration of the optic nerve, leading to pallor of the optic disc, reduced visual function, and permanent vision loss.

Causes

- **Primary Optic Atrophy** (Direct damage to optic nerve):
  - **Optic neuritis** (e.g., multiple sclerosis).
  - Trauma to the optic nerve.
  - **Ischemic** optic neuropathy (e.g., giant cell arteritis, non-arteritic causes).

- Glaucoma.
- **Hereditary conditions** (e.g., **Leber's hereditary optic neuropathy**). DIDMOAD - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)
- **Toxic or nutritional** optic neuropathy (e.g., methanol poisoning, vitamin B12 deficiency).

- **Secondary Optic Atrophy** (Due to prolonged swelling of optic disc):
  - Papilledema (e.g., raised intracranial pressure).
  - Chronic optic neuritis.
  - Compression by tumors (e.g., pituitary adenoma, meningioma).
- **Other Causes**:
  - Retinal diseases (e.g., central retinal artery occlusion).
  - Infection or inflammation (e.g., neurosyphilis, tuberculosis).

Clinical Features

- **Vision Loss**:
  - Gradual, progressive decline in visual acuity (may be central or peripheral).
  - Visual field defects (e.g., central scotoma or altitudinal defects).
- **Colour Vision Impairment**:
  - Reduced ability to distinguish colours (dyschromatopsia).
- **Optic Disc Pallor**:
  - Observed on fundoscopy (white or pale disc due to loss of axons).
- **Relative Afferent Pupillary Defect (RAPD)**:
  - Present in unilateral or asymmetric optic nerve damage.

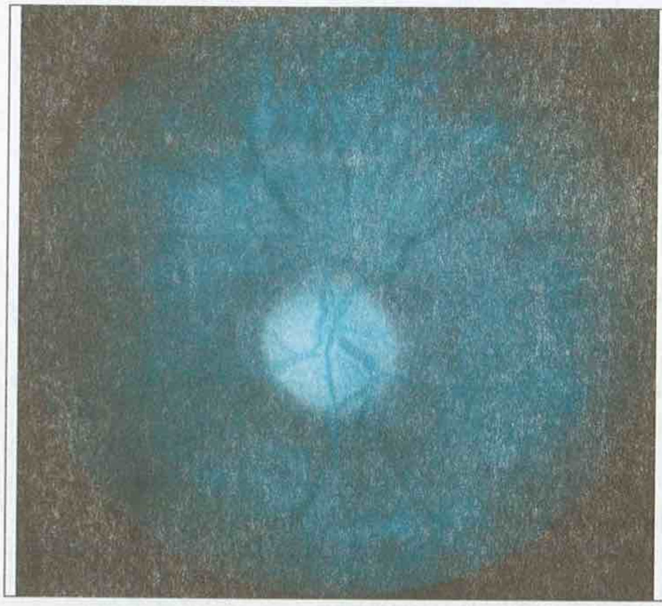
Diagnosis

- **Ophthalmoscopy**: Pale optic disc with sharp or blurred margins.
- **Visual Field Testing**: Detects characteristic field defects.
- **Colour Vision Testing**: Reduced colour discrimination.
- **Imaging: MRI/CT of the brain and orbits**: Rule out compressive or structural lesions.
- **Blood Tests**: For inflammatory, infectious, or toxic causes (e.g., ESR, syphilis serology, B12 levels).

Management

- **Treat Underlying Cause**:
  - E.g., steroids for optic neuritis, surgery for compressive lesions, correction of nutritional deficiencies.
- **Supportive Measures**:
  - Low-vision aids (e.g., magnifiers, electronic devices).
  - Vision rehabilitation.
- **Prevent Progression**:
  - Address risk factors like smoking and toxins.

Prognosis: Vision loss is typically irreversible, but progression can sometimes be halted.



This patient has **optic atrophy** as revealed by a particularly **pale disc**. Causes include:

- **Glaucoma**
- External compression of the optic nerves, for example, pituitary tumour, and
- Multiple sclerosis.

Optic Neuritis

Definition

- Optic neuritis is an acute inflammatory condition of the optic nerve that causes vision loss, often associated with pain on eye movement.

Causes

- **Idiopathic: Most common.**
- **Demyelinating Disorders**:
  - **Multiple sclerosis (MS)** (**most common association**).
  - Neuromyelitis optica spectrum disorder (NMOSD).
- **Infectious**:
  - Viral: Herpes simplex, varicella-zoster virus.
  - Bacterial: Syphilis, tuberculosis, Lyme disease.
  - Fungal: Cryptococcus.
- **Autoimmune**:
  - Systemic lupus erythematosus.
  - Sarcoidosis.
- **Toxic and Nutritional**:
  - Methanol poisoning.
  - Vitamin B12 deficiency.
- **Post-Viral or Post-Vaccination.**

Clinical Features

- **Visual Symptoms**:
  - Sudden onset of **monocular vision loss.**
  - Severity varies from mild blurring to complete blindness.
  - Vision loss worsens over hours to days.

- **Pain**: Eye pain, especially with movement.
- **Visual Field Defects**: Central or paracentral scotomas.
- **Colour Vision Impairment**: Desaturation, especially red colours.
- **Relative Afferent Pupillary Defect (RAPD)**: Present in unilateral or asymmetric optic neuritis.
- **Fundoscopy**:
    - **Normal optic disc (retrobulbar neuritis)** in ~2/3 of cases.
    - **Swollen disc (papillitis)** in ~1/3 of cases.

Diagnosis

- **MRI of Brain and Orbits with Gadolinium**:
    - Detects optic nerve inflammation.
    - Assesses for white matter lesions suggestive of MS.
- **Visual Evoked Potentials (VEP)**:
    - Demonstrates delayed conduction in the optic nerve.
- **Laboratory Tests**:
    - Screen for systemic and infectious causes (e.g., ANA, ESR, syphilis serology, B12 levels).

Management

- **Pharmacological Treatment**:
    - **High-dose intravenous corticosteroids (e.g., Methylprednisolone 1 g/day for 3 days)**:
        - Speeds up recovery but does not alter final visual outcome.
        - Oral steroids alone are not recommended as they may increase relapse risk.
- **Treat Underlying Cause**:
    - E.g., antibiotics for infections, immunosuppressants for autoimmune conditions.

Prognosis

- Most patients recover vision **spontaneously within weeks to months**.
- Poor prognostic factors:
    - Severe vision loss at onset.
    - Lack of recovery after 1 month.
    - Associated systemic disease (e.g., NMOSD).

Optic neuritis

- **very rare in people over the age of 50.**
- **The patient sees nothing and the doctor sees nothing**
- Visual loss typically **occurs over days rather than hours**
- **Presents with a particular type of central visual loss - a central scotoma.**
- **Optic disc is swollen**
- **The retrobulbar neuritis seen with ethambutol may be unilateral or bilateral; as such unilateral symptoms do not preclude the diagnosis.**
- **Most cases of optic neuritis are retrobulbar and hence there are no abnormalities on fundoscopy. the most likely finding on fundoscopy → Normal optic disc**
- **MRI with gadolinium of the brain** will likely show → **enhancement of the optic nerve**
- **Abnormal visual evoked potentials (VEP)**

Relative Afferent Pupillary Defect (RAPD)

Definition

- A **Relative Afferent Pupillary Defect (RAPD)**, also called a **Marcus Gunn pupil**, occurs when one optic nerve or retina transmits a weaker afferent (sensory) signal to the brain compared to the other, resulting in an abnormal pupillary light reflex.

Pathway of pupillary light reflex

- Afferent: retina → optic nerve → lateral geniculate body → midbrain
- Efferent: Edinger-Westphal nucleus (midbrain) → oculomotor nerve

Pathophysiology

- The **afferent pathway** of the pupillary reflex involves light detection in the retina, the optic nerve, and neural pathways up to the pretectal area in the midbrain.
- In RAPD:
  - Light shone in the affected eye produces a reduced pupillary constriction due to the weaker afferent signal.
  - Light shone in the unaffected eye produces a normal pupillary constriction.

Causes

- **Optic Nerve Lesions**:
  - Optic neuritis (e.g., in multiple sclerosis).
  - Ischemic optic neuropathy.
  - Optic nerve compression (tumors, trauma).
- **Retinal Disorders**:
  - Central retinal artery occlusion.
  - Central retinal vein occlusion.
  - Large retinal detachment.
- **Asymmetrical Chiasmal Disease**:
  - Tumors causing partial chiasmal compression.
- **Advanced Glaucoma**:
  - If asymmetrical damage to optic nerve fibers.

Clinical Features

- **Pupillary Light Reflex**:
  - When light is shone into the unaffected eye:
    - Both pupils constrict normally.
  - When light is shone into the affected eye:
    - Both pupils dilate slightly or show reduced constriction.
- No anisocoria (pupils are of equal size in light and dark).
- Often associated with **visual symptoms** if caused by optic nerve or retinal disease.

Testing for RAPD

- **Swinging Flashlight Test**:
  1. Instruct the patient to look at a distant object in a dimly lit room.
  2. Shine a bright light into one eye for 1-2 seconds, then quickly switch to the other eye.
  3. Observe the pupillary response in both eyes.
  4. Findings:
     - **Normal**: Both pupils constrict equally when light is shone into either eye.
     - **RAPD**: Pupils constrict less or dilate when light is shone into the affected eye.

Clinical Significance

- Indicates **unilateral or asymmetric optic nerve or severe retinal dysfunction**.
- Does **not occur** in:
  - Bilateral symmetric optic nerve disease.
  - Pure efferent pathway disorders (e.g., third nerve palsy).

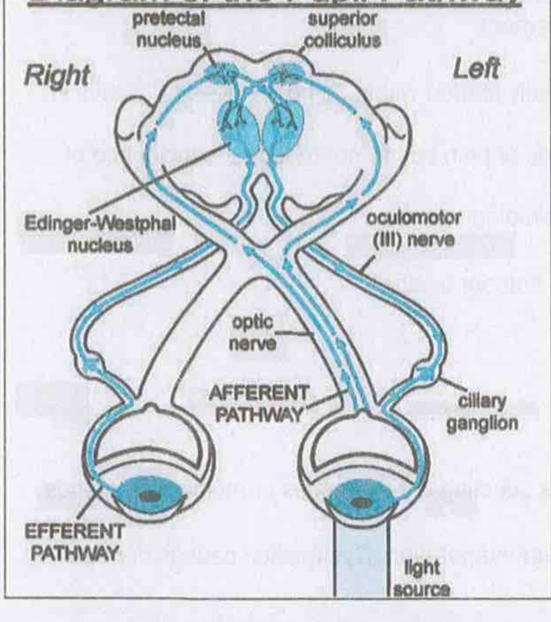
Management

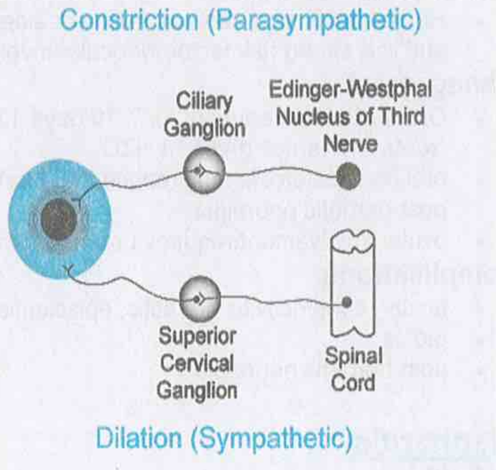
- Identify and treat the **underlying cause**:
  - Optic neuritis: Corticosteroids (e.g., methylprednisolone).
  - Retinal vascular occlusions: Manage vascular risk factors and specific retinal treatments.
  - Compressive optic neuropathies: Surgical decompression or treatment of the mass.
- **Supportive Care**: Low-vision aids for persistent visual loss.

Key Points for MRCP Candidates

1. RAPD is detected using the **swinging flashlight test**.
2. Common causes include **optic neuritis**, **ischemic optic neuropathy**, and **retinal vascular occlusions**.
3. RAPD is a hallmark of **afferent pathway defects** and does not occur in purely efferent lesions.

Diagram of the Pupil Pathway





due to the consensual response of the pupillary light reflex, shining light in the unaffected eye will produce bilateral miosis.

⇨ shining light in the affected eye will not produce miosis because the afferent limb of the pupillary light reflex pathway is damaged (eg: optic neuritis)

⇨ However, **due to the bilateral projections of nerves from the Edinger-Westphal nucleus**, light shined in the **unaffected eye** will produce **bilateral miosis**. This phenomenon is called a **consensual response**.

Herpes simplex keratitis

- Herpes simplex keratitis most commonly presents with a dendritic corneal ulcer

Features

- red, painful eye
- photophobia
- epiphora
- visual acuity may be decreased
- fluorescein staining may show an epithelial ulcer (dendritic corneal ulcer)

Management

- immediate referral to an ophthalmologist
- topical aciclovir

Herpes zoster ophthalmicus

Definition

- Herpes zoster ophthalmicus (HZO) describes the reactivation of the varicella zoster virus in the area supplied by the ophthalmic division of the trigeminal nerve.
- It accounts for around 10% of case of shingles.

Features

- vesicular rash around the eye, which may or may not involve the actual eye itself
- Hutchinson's sign: rash on the tip or side of the nose. Indicates nasociliary involvement and is a strong risk factor for ocular involvement

Management

- **Oral antiviral** treatment for 7-10 days, ideally started within 72 hours. **Topical antiviral treatment is not given in HZO**
- oral corticosteroids may reduce the duration of pain but do not reduce the incidence of post-herpetic neuralgia
- ocular involvement requires urgent ophthalmology review

Complications

- ocular: conjunctivitis, keratitis, episcleritis, anterior uveitis
- ptosis
- post-herpetic neuralgia

Blepharitis

Definition

- Chronic inflammation of the eyelid margins affecting the eyelashes or meibomian glands.

Pathophysiology

- Meibomian glands secrete oil to prevent tear evaporation. Dysfunction causes dry eyes, leading to irritation.

Types

- **Anterior blepharitis**: Affects eyelashes; linked to **Staphylococcus aureus** or seborrheic dermatitis.(less common).
- **Posterior blepharitis**: Involves meibomian glands; associated with rosacea or gland dysfunction.(common).

Symptoms
- Red, swollen eyelid margins.
- Gritty sensation, itching, or burning.
- Crusting around eyelashes.
- Dry eyes.
- **Associated conditions:**
  - **More common in patients with rosacea.**
  - Increased styes and chalazions.
  - Secondary conjunctivitis.

Management
- **Symptom Relief**:
  - Artificial tears for dry eyes or abnormal tear film.
- **Eyelid Hygiene**:
  - Warm compresses, gentle cleaning with diluted baby shampoo.
- **Medications**:
  - Topical antibiotics (e.g., erythromycin).
  - Oral doxycycline for severe cases.
  - Artificial tears for dry eyes.
- **Treat underlying conditions** (e.g., rosacea).

Key Points
- Blepharitis is chronic and requires regular lid hygiene.
- Associated with **rosacea** and **dry eye syndrome**.

Keratitis
Definition
- Keratitis is an inflammation of the cornea, which may result in pain, redness, visual impairment, and in severe cases, corneal scarring or perforation.

Types and Causes
- **Infectious Keratitis**:
  - **Bacterial**: *Staphylococcus aureus, Pseudomonas aeruginosa* (common in contact lens users).
  - **Viral**: Herpes simplex virus (HSV), varicella-zoster virus.
  - **Fungal**: *Aspergillus, Candida* (associated with trauma or plant material exposure).
  - **Parasitic**: *Acanthamoeba* (contact lens misuse, contaminated water).
- **Non-Infectious Keratitis**:
  - Dry eye syndrome.
  - Allergic or autoimmune conditions (e.g., Sjögren's syndrome).
  - Exposure keratitis (e.g., incomplete eyelid closure in Bell's palsy).
  - Chemical or UV light injury.

Clinical Features
- **Symptoms**:
  - Eye pain and redness.
  - Photophobia (light sensitivity).
  - Blurred vision.
  - Foreign body sensation.
  - Excessive tearing or discharge.

- **Signs**:
  - Corneal ulcer or epithelial defect (visible on fluorescein staining).
  - Hypopyon (pus in anterior chamber, in severe cases).
  - Decreased corneal clarity or opacity.

Diagnosis

- **Clinical Examination**:
  - Slit-lamp examination with fluorescein staining to identify corneal defects or ulcers.
- **Microbiological Studies**:
  - Corneal scrapings for bacterial, fungal, or viral cultures in infectious cases.
- **Imaging**:
  - Confocal microscopy for *Acanthamoeba keratitis*.

Management

- **Infectious Keratitis**:
  - **Bacterial**: Topical antibiotics (e.g., moxifloxacin or ciprofloxacin eye drops). Severe cases may need systemic antibiotics.
  - **Viral**: Topical antivirals (e.g., acyclovir ointment) and oral antivirals if necessary.
  - **Fungal**: Topical antifungals (e.g., natamycin) ± systemic antifungals.
  - **Parasitic**: Antiparasitic agents (e.g., chlorhexidine or polyhexamethylene biguanide).
- **Non-Infectious Keratitis**:
  - Lubricating eye drops for dry eyes.
  - Protective measures (e.g., eyelid tape for exposure keratitis).
  - Corticosteroid eye drops for autoimmune-related keratitis (under specialist care).
- **Severe Cases**:
  - Hospitalization for frequent treatments.
  - Surgery (e.g., corneal transplant) for perforation or severe scarring.

Complications

- Corneal scarring.
- Vision loss.
- Corneal perforation.
- Endophthalmitis (intraocular infection).

Key Points

- **Urgent ophthalmologic referral** is essential in suspected keratitis.
- Contact lens wearers are at high risk of bacterial and *Acanthamoeba* keratitis.

- *Pseudomonas aeruginosa* is commonly associated with contact lens related infections.
- The management must also include advising the patient to discontinue wearing contact lenses and referral to a specialist ophthalmic unit.
- Recurrence is common.

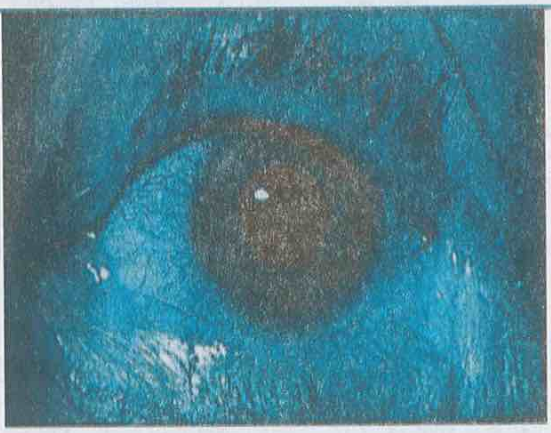
Keratitis

- Sharp ocular pain
- **Pseudomonas aeruginosa is commonly associated with contact lens related infections.**
- **The management involve discontinue wearing contact lenses and referral to a specialist ophthalmic unit.**
- **Recurrence is common.**

Keratitis overview		
	Characteristic features	**Therapy**
Bacterial keratitis (typically Staph. aureus Pseudomonas is seen in contact lens wearers.)	➲ **Most common form of keratitis** ➲ ↑ Risk with wearing contact lenses ➲ Purulent discharge and/or hypopyon ➲ Round corneal infiltrate or ulcer	Topical broad-spectrum antibiotics (e.g., ciprofloxacin)
Herpes zoster keratitis	➲ ↓ Corneal sensation ➲ **Punctate lesions** on the corneal surface (early disease) ➲ Vesicular eruption on forehead, bridge, and tip of the nose	➲ Oral acyclovir, valacyclovir, or famciclovir ➲ Topical steroids
Herpes simplex keratitis	Dendritic or geographic corneal ulcer	Topical trifluridine or ganciclovir
Acanthamoeba keratitis	➲ ↑ Risk with wearing **contact lenses** ➲ Corneal ring infiltrate	Topical antiseptic (e.g., chlorhexidine) with propamidine

Dendritic ulcers

- **caused by** herpes simplex virus.
- **Presentation** is usually with pain, photophobia, blurred vision, conjunctivitis and chemosis.
- Steroid eye drops are contraindicated as they may induce massive amoeboid ulceration and blindness.
- **treated with aciclovir eye drops,** which should be continued for three days after the ulcer has healed.



Red eye

Differential Diagnosis

Condition	Diagnostic Features	Treatment
Conjunctivitis	- Diffuse redness, watery (viral) or purulent (bacterial) discharge. - No pain or vision loss.	- Viral: Supportive (artificial tears, hygiene). - Bacterial: Topical antibiotics (e.g., chloramphenicol).
Keratitis	- Pain, photophobia, decreased vision. - Fluorescein staining shows corneal ulcer/defect.	- Bacterial: Topical antibiotics (e.g., moxifloxacin). - Viral: Acyclovir ointment ± oral antivirals.
Anterior Uveitis	- Deep aching pain, photophobia, blurred vision. - Slit-lamp: Cells/flare in anterior chamber.	- Topical steroids (e.g., prednisolone drops). - Cycloplegics (e.g., atropine) for pain relief.
Acute Angle Closure Glaucoma (AACG)	- Severe pain, nausea/vomiting, blurred vision. - Fixed mid-dilated pupil, hazy cornea, high IOP.	- Emergency: Acetazolamide (IV/PO), mannitol, pilocarpine (after IOP control). - Definitive: Laser iridotomy.
Scleritis	- Severe deep eye pain (worse with eye movement). - Localised or diffuse scleral redness.	- Systemic NSAIDs (e.g., ibuprofen). - Severe: Systemic corticosteroids or immunosuppressants.
Episcleritis	- Mild pain, sectoral redness. - No vision loss. - Blanches with phenylephrine drops.	- Supportive: Artificial tears. - Severe: Topical NSAIDs or steroids.
Subconjunctival Hemorrhage	- Bright red patch on sclera, painless. - Normal vision and no discharge.	- None required (self-limiting). - Address underlying cause (e.g., hypertension, anticoagulants).
Blepharitis	- Red, swollen eyelid margins. - Crusting around lashes, grittiness.	- Lid hygiene: Warm compresses and cleaning. - Topical antibiotics (e.g., fusidic acid) if infection.
Dry Eye Syndrome	- Mild redness, gritty sensation, worsens with prolonged visual tasks.	- Artificial tears. - Address underlying causes (e.g., meibomian gland dysfunction).
Foreign Body	- Sudden pain, tearing, foreign body sensation. - Visible foreign object or corneal abrasion (fluorescein).	- Remove foreign body. - Lubricating drops or antibiotics for abrasions (e.g., chloramphenicol).
Chemical Injury	- History of chemical exposure. - Redness, pain, blurred vision, epithelial damage on staining.	- Immediate irrigation with saline/water. - Topical antibiotics and ophthalmology referral.

Condition	Diagnostic Features	Treatment
Trauma	- History of injury. - Lid swelling, subconjunctival hemorrhage, or corneal abrasion (fluorescein).	- Manage based on injury type (e.g., repair lacerations, antibiotics for abrasion).
Allergic Conjunctivitis	- Bilateral itching, tearing, redness, and chemosis.	- Antihistamine/mast cell stabiliser drops (e.g., olopatadine).

Key Points
- **Urgent conditions** (e.g., AACG, keratitis, scleritis) require immediate ophthalmology referral.
- Fluorescein staining is essential for identifying corneal defects.

Red eye - glaucoma or uveitis?
- glaucoma: severe pain, haloes, 'semi-dilated' pupil
- uveitis: small, fixed oval pupil, ciliary flush

Anterior Uveitis
Definition: Inflammation of the iris and ciliary body.

Causes
- **Idiopathic** (most common).
- **Autoimmune**: HLA-B27 diseases (e.g., ankylosing spondylitis).
- **Infectious**: Herpes simplex, syphilis.
- **Trauma**.

Clinical Features
- **Pain**, **redness**, and **photophobia**.
- Blurred vision, ciliary flush, and irregular pupil.
- **Slit-lamp**: Cells/flare in anterior chamber.

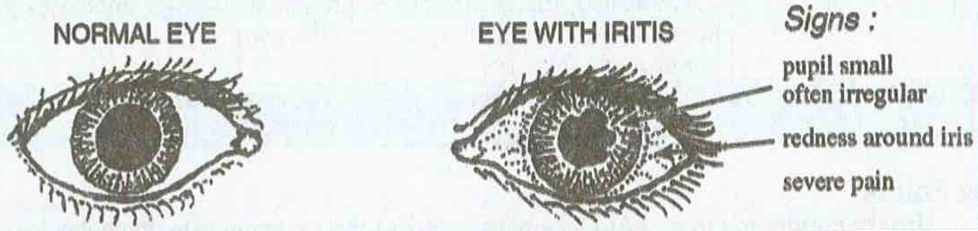
Management
- **Topical corticosteroids**: Reduce inflammation.
- **Cycloplegics**: Relieve pain and prevent synechiae.
- Treat underlying cause if identified.

Key Points
- Strong link with **HLA-B27** diseases.
- Requires **urgent referral** to prevent complications like glaucoma or cataracts.

Iritis is a form of anterior uveitis, but they are not exactly the same:
- **Anterior Uveitis: Refers to inflammation of the anterior uveal tract, which includes both the iris and the ciliary body.**
- **Iritis: Specifically refers to inflammation limited to the iris.**

In clinical practice, the terms are often used interchangeably because iritis is the most common form of anterior uveitis. However, anterior uveitis can also include iridocyclitis, where both the iris and ciliary body are inflamed.

IRITIS (INFLAMMATION OF THE IRIS)



Scleritis

Definition

- Inflammation of the sclera, often associated with systemic autoimmune diseases.

Causes

- **Autoimmune**: Rheumatoid arthritis, granulomatosis with polyangiitis.
- **Infectious**: Herpes zoster, tuberculosis, syphilis.

Clinical Features

- Severe, deep **eye pain** (worse with movement).
- **Redness**: Diffuse or nodular scleral inflammation.
- May have decreased vision.

Management

- **Should be referred urgently to the ophthalmology clinic**
- **Systemic NSAIDs** (e.g., ibuprofen).
- Severe cases: **Systemic corticosteroids** or immunosuppressants.
- Treat underlying disease.

Key Points

- Severe pain distinguishes it from episcleritis.
- **Rheumatoid arthritis is the most common cause**
- Requires **systemic treatment**; refer to ophthalmology.

Episcleritis

Definition

- Inflammation of the episclera, the layer between the conjunctiva and sclera. It is usually **benign and self-limiting**.

Causes

- **Idiopathic** (most common).
- Associated with systemic diseases: Rheumatoid arthritis, lupus, inflammatory bowel disease.

Clinical Features

- Mild **redness** (often sectoral).
- Mild **pain** or discomfort (not severe).
- No vision loss.
- Blanches with phenylephrine drops (distinguishes from scleritis).

Management
- Usually self-resolving.
- **Artificial tears** for symptom relief.
- Severe cases: **Topical NSAIDs** or corticosteroids.

Key Points
- **Painless or mildly painful** redness.
- Distinguished from scleritis by **lack of severe pain** and self-limiting course.

Scleritis is painful, episcleritis is not painful

Conjunctivitis

Definition
- Inflammation of the conjunctiva, often causing **redness**, **discharge**, and **discomfort**.

Types and Causes
- **Viral**:
  - Commonly caused by *adenovirus*.
  - Features: Watery discharge, preauricular lymphadenopathy, highly contagious.
- **Bacterial**:
  - Common pathogens: *Staphylococcus aureus, Streptococcus pneumoniae*.
  - Features: Purulent discharge, eyelids stuck together in the morning.
- **Allergic**:
  - Triggered by allergens.
  - Features: Itchy, watery eyes with chemosis (swelling of conjunctiva).

Clinical Features
- Redness (diffuse conjunctival injection).
- Discharge: Watery (viral/allergic) or purulent (bacterial).
- No significant pain or vision loss.

Management
- **Viral**: Supportive (artificial tears, hygiene).
- **Bacterial**: Topical antibiotics (e.g., chloramphenicol).
- **Allergic**: Antihistamine or mast cell stabilisers (e.g., olopatadine).

Key Points
- **Highly contagious** in viral and bacterial forms.
- Distinguish from more serious red-eye conditions by **absence of pain or vision loss**.

Subconjunctival Haemorrhage

Definition
- Bleeding beneath the conjunctiva, appearing as a well-demarcated red patch on the sclera.

Causes
- **Spontaneous**: Often idiopathic or due to minor trauma (e.g., rubbing eyes).
- **Increased venous pressure**: Coughing, sneezing, vomiting, straining.
- **Trauma**: Eye injury, surgery.
- **Systemic conditions**:
  - Hypertension.
  - Bleeding disorders (e.g., anticoagulant use).

Clinical Features

- Bright red, painless patch on the sclera.
- No discharge or vision changes.
- Resolves over 1–2 weeks as blood is reabsorbed.

Management

- **Reassurance**: Self-limiting in most cases.
- Treat underlying cause (e.g., hypertension control, review anticoagulants).

Key Points

- **Painless and isolated redness** distinguishes it from other red-eye conditions.
- No specific treatment required unless recurrent or associated with systemic disease.

Posterior Uveitis

Definition

- Inflammation of the posterior segment of the eye, involving the retina, choroid, or both.

Causes

- **Infectious**:
  - Toxoplasmosis (most common).
  - Cytomegalovirus (CMV), herpes simplex, syphilis, tuberculosis.
- **Non-Infectious**:
  - Autoimmune diseases (e.g., sarcoidosis, Behçet's disease).
  - Idiopathic.

Clinical Features

- **Blurred vision** (most common symptom).
- Floaters.
- **Minimal redness** or pain (may be absent).
- Fundoscopy: Retinal lesions, choroidal inflammation, or vasculitis.

Diagnosis

- **Fundoscopy/Slit-lamp exam**: Inflammatory changes in the posterior segment.
- Imaging: Optical coherence tomography (OCT), fluorescein angiography.
- **Blood tests**: Identify systemic or infectious causes (e.g., toxoplasmosis serology, ANA, syphilis screening).

Management

- **Infectious Causes**:
  - Toxoplasmosis: Oral pyrimethamine and sulfadiazine + folinic acid.
  - CMV: Intravitreal or systemic antivirals (e.g., ganciclovir).
- **Non-Infectious Causes**:
  - **Corticosteroids**: Oral or intravitreal for inflammation.
  - **Immunosuppressive agents** (e.g., methotrexate) for refractory cases.

Complications

- Retinal detachment.
- Optic nerve damage.
- Permanent vision loss.

Key Points

- Posterior uveitis commonly presents with **blurred vision** and floaters.
- Fundoscopy and targeted investigations are essential to identify the underlying cause.
- Treatment depends on the etiology (infectious vs. autoimmune).

Retinitis

Definition

- Inflammation of the retina, leading to retinal dysfunction and vision impairment. It can occur alone or as part of posterior uveitis.

Causes

- **Infectious**:
  - Viral: Cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV).
  - Parasitic: Toxoplasmosis.
  - Bacterial: Syphilis, tuberculosis.
- **Non-Infectious**:
  - Autoimmune conditions (e.g., Behçet's disease, sarcoidosis).

Clinical Features

- **Painless vision loss** or blurring.
- Floaters and scotomas (blind spots).
- May have systemic symptoms (e.g., fever in infectious causes).
- Fundoscopy:
  - Retinal whitening or necrosis (e.g., CMV retinitis).
  - Retinal hemorrhages (in severe cases).

Diagnosis

- **Fundoscopy**: Retinal lesions, hemorrhages, or necrosis.
- Imaging: Optical coherence tomography (OCT) or fluorescein angiography.
- **Blood tests**: Identify infectious causes (e.g., toxoplasmosis serology, HIV testing for CMV).

Management

- **Infectious Causes**:
  - CMV: Systemic or intravitreal ganciclovir.
  - HSV/VZV: Oral or intravenous acyclovir.
  - Toxoplasmosis: Pyrimethamine, sulfadiazine, and folinic acid.
- **Non-Infectious Causes**:
  - Corticosteroids (systemic or intravitreal).
  - Immunosuppressive therapy for autoimmune retinitis.

Complications

- Retinal detachment.
- Vision loss (partial or complete).

Key Points

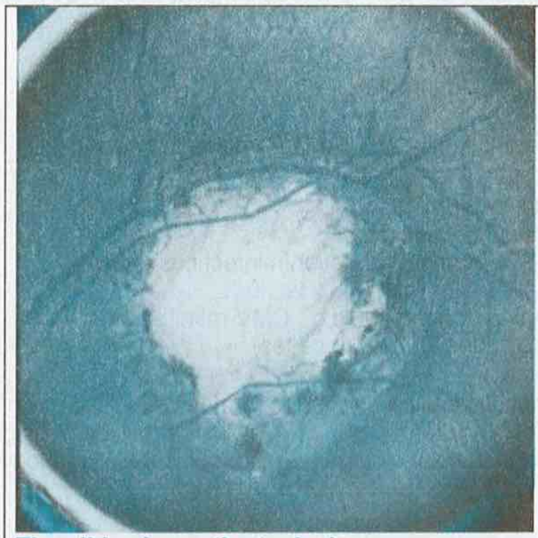
- **CMV retinitis** is common in immunocompromised patients (e.g., HIV/AIDS).
- Fundoscopy reveals characteristic retinal lesions that guide diagnosis.
- Treatment focuses on **targeting the underlying cause** to prevent vision loss.

Cytomegalovirus (CMV) Retinitis:

- **A sight-threatening retinal infection caused by cytomegalovirus, primarily affecting immunocompromised patients (e.g., HIV/AIDS).**
- The most common cause of vision loss in AIDS patients.
- **It presents with painless vision loss, floaters, and characteristic retinal whitening with hemorrhages on fundoscopy.**
- Fundoscopy → 'brushfire-like' lesion (a large patch of white fluffy lesion mixed with extensive retinal haemorrhages)
- **Treatment involves systemic or intravitreal antivirals (e.g., ganciclovir).**

Toxocara Retinitis:

- **A parasitic retinal infection caused by *Toxocara canis* or *Toxocara cati*, often in children exposed to contaminated soil or pets.**
- **It presents with unilateral vision loss, retinal granulomas, and vitritis.**
- **There is usually only a single, well demarcated lesion.**
- **Treatment includes anti-parasitic therapy (e.g., albendazole) and corticosteroids to reduce inflammation.**



The slide shows the typical appearance of *Toxocara* retinitis with a lesion at the macula.

Retinitis Pigmentosa (RP)

Definition:

- A group of inherited retinal dystrophies characterized by progressive degeneration of photoreceptors, primarily affecting rods and cones.

Pathophysiology:

- **Degeneration of Rod Photoreceptors:**
  - Rod cells, located in the **peripheral retina**, are responsible for **dim light vision**.
  - Early degeneration leads to **night blindness** and **loss of peripheral vision**.
- **Degeneration of Cone Photoreceptors:**
  - Cone cells, concentrated in the **central retina (macula)**, are essential for **fine visual detail** and **color perception**.
  - Cone loss occurs in **late stages**, causing **central vision loss** and **color blindness**.

Clinical Features:

- **Night blindness** (early symptom due to rod dysfunction).
- Progressive **peripheral vision loss** ("tunnel vision").
- **Central vision loss** in advanced stages.
- Fundoscopy: Bone spicule pigmentation, attenuated retinal vessels, pale optic disc.

Associated Diseases

- **Genetic and Syndromic Associations**:
  - **Refsum Disease**: Features include cerebellar ataxia, peripheral neuropathy, deafness, and ichthyosis.
  - **Usher Syndrome**: Combination of hearing loss and retinitis pigmentosa.
  - **Abetalipoproteinemia**: Fat malabsorption, ataxia, and retinitis pigmentosa.
  - **Lawrence-Moon-Biedl Syndrome**: Obesity, polydactyly, hypogonadism, and retinitis pigmentosa.
  - **Kearns-Sayre Syndrome**: Progressive external ophthalmoplegia, cardiac conduction defects, and retinitis pigmentosa.
  - **Alport Syndrome**: Hearing loss, kidney disease, and retinitis pigmentosa.
  - **Mitochondrial Myopathy**: Mitochondrial dysfunction affecting multiple systems, including the retina.
- **Drug-Induced**:
  - **Thioridazine**: Causes retinal deposits resembling retinitis pigmentosa.
    - Withdrawn due to severe cardiac arrhythmias.
    - Important to differentiate from **chlorpromazine**, which causes corneal deposits, not retinal deposits.

Diagnosis:

- **Electroretinography (ERG)**: Reduced rod and cone responses.
- **Genetic testing**: Identifies mutations in causative genes.

Management:

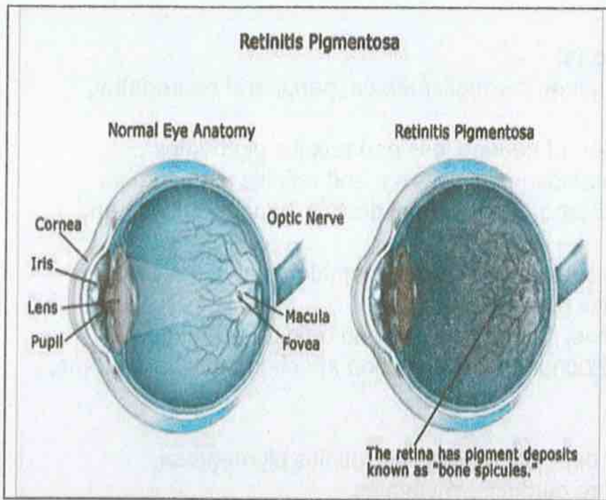
- **No cure**, but supportive measures include:
  - Vitamin A supplementation (controversial).
  - Low-vision aids.
  - Gene therapy trials (emerging).

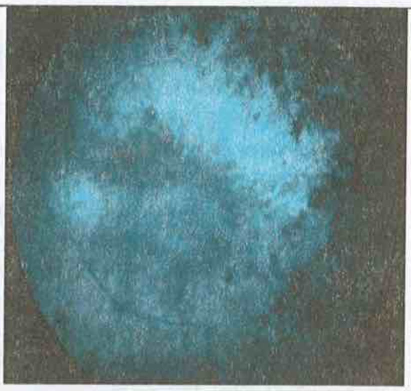
Key Point:

- RP is a progressive, incurable condition leading to blindness, often identified by night blindness and peripheral vision loss.
- **Rods die first**, leading to early symptoms of night blindness.
- **Cones die later**, causing progressive central vision loss.

> Retinitis pigmentosa - night blindness + funnel vision

> Thioridazine → <u>**retinal**</u> deposits (**retinitis pigmentosa**).
> chlorpromazine → <u>corneal</u> deposits





Fundus showing changes secondary to retinitis pigmentosa

Sudden painless loss of vision

Differential Diagnosis of Sudden Painless Loss of Vision

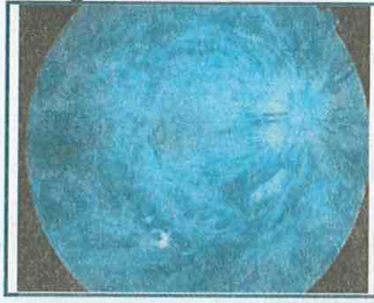
Condition	Diagnostic Features	Treatment
Retinal Artery Occlusion	- Sudden, complete vision loss. - Pale retina with a cherry-red spot on fundoscopy.	- Ocular massage, anterior chamber paracentesis. - Immediate referral for thrombolysis or surgery.
Retinal Vein Occlusion	- **More common than arterial occlusion** - Painless blurred vision or loss. - Fundoscopy: "Blood and thunder" appearance with retinal hemorrhages.	- Manage underlying conditions (e.g., hypertension, diabetes). - Intravitreal anti-VEGF (e.g., ranibizumab).
Vitreous Hemorrhage	- Sudden vision loss, often described as a "curtain" or dark floaters. - Fundoscopy: Poor retinal visualization due to blood.	- Identify and treat cause (e.g., proliferative diabetic retinopathy). - Vitrectomy if severe.
Retinal Detachment	- Peripheral vision loss ("curtain coming down"). - Fundoscopy: Detached, wrinkled retina.	- Immediate surgical repair (e.g., vitrectomy, scleral buckle).
Optic Neuritis	- Unilateral vision loss, often painful. - RAPD and optic disc swelling (sometimes retrobulbar).	- High-dose corticosteroids (e.g., IV methylprednisolone).

Condition	Diagnostic Features	Treatment
Ischemic Optic Neuropathy	- Painless vision loss, typically unilateral. - Fundoscopy: Pale, swollen optic disc (arteritic form).	- Arteritic: High-dose corticosteroids immediately (e.g., in giant cell arteritis).
Central Serous Retinopathy	- Sudden blurred vision with central scotoma. - Fundoscopy/OCT: Subretinal fluid accumulation.	- Observation (most cases resolve spontaneously). - Laser or anti-VEGF for persistent cases.
Acute Macular Degeneration	- Sudden loss of central vision. - Fundoscopy: Subretinal hemorrhage or exudates.	- Intravitreal anti-VEGF (e.g., bevacizumab).
Functional Vision Loss	- Inconsistent visual complaints. - Normal ocular examination findings.	- Psychological evaluation and reassurance.

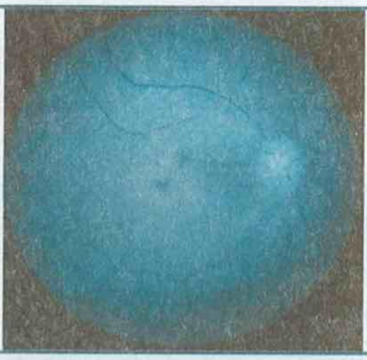
Amaurosis Fugax

Aspect	Details
Definition	Sudden, painless, transient loss of vision, typically lasting seconds to minutes, followed by spontaneous recovery.
Cause	Retinal ischemia due to transient occlusion of the central retinal artery by microemboli.
Risk Factors	- Atherosclerosis - Carotid artery stenosis - Cardiac emboli (e.g., atrial fibrillation) - Hypercoagulable states
Features	- Unilateral vision loss ("black curtain" descending over vision). - Complete recovery of vision within minutes.
Complications	- Indicates a high risk of **Transient Ischemic Attack (TIA)** or **stroke**.
Diagnosis	- Clinical history and exam. - Carotid Doppler to assess for carotid stenosis. - Echocardiography for cardiac embolic sources. - Blood tests for hypercoagulable states.
Treatment	- Address underlying cause: - **Antiplatelets** (e.g., aspirin) for atherosclerosis. - **Anticoagulation** for atrial fibrillation.
Prevention	- Manage risk factors: - Control hypertension, diabetes, and hyperlipidemia. - Smoking cessation.

Images

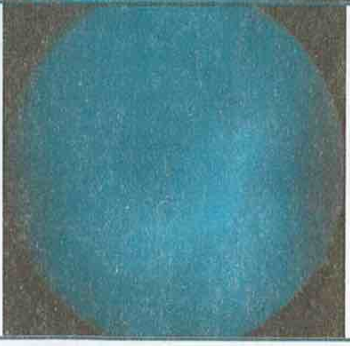


Central vein occlusion:
Flame-shaped hemorrhage is visible in all four retinal quadrants.



Central retinal artery occlusion:
Narrow retinal arteries and a pale retina with early signs of nerve fiber layer edema are visible.
The fovea centralis appears red (cherry-red spot; due to the transparency of the well-vascularized choroid, as no nerve fibers are present in the fovea avascular zone. Therefore, there is no edema.

Retinal detachment:
The retina is visible as a yellow-grey, bullous elevation in the upper part of the image.
- Green overlay: detached retina
- Red overlay: tear



Fundus Photograph of Vitreous Haemorrhage

Central retinal vein occlusion - sudden painless loss of vision, severe retinal haemorrhages on fundoscopy

Flashes and floaters - vitreous/retinal detachment

An elderly patient with acute visual loss has giant cell arteritis until proved otherwise

The history of diabetes, complete loss of vision in the affected eye and inability to visualise the retina point towards a diagnosis of vitreous haemorrhage.

Nasal branch retinal vein occlusion → sudden blurring (not total visual loss) of the temporal field in the affected eye.

Of all types of retinal vessel occlusion, ischemic Central Retinal Vein Occlusion is most commonly associated with neovascularization.

Tunnel Vision

Definition:

- Constriction of the visual field, leading to a "tunnel-like" vision where peripheral vision is lost but central vision remains intact.

Causes:

- **Ophthalmic Causes:**
  - Advanced glaucoma (progressive optic nerve damage).
  - Retinitis pigmentosa (degenerative retinal condition).
- **Neurological Causes:**
  - Compression of the optic chiasm (e.g., pituitary tumors).
  - Stroke or ischemic damage to the visual pathway.
- **Functional Causes:**
  - Psychogenic visual disturbances (non-organic causes).

Clinical Features:

- Peripheral vision loss.
- Difficulty navigating in dim light or crowded spaces.
- May bump into objects due to impaired side vision.

Eye Signs in Systemic Diseases

Condition	Eye Signs	Additional Notes
Neurofibromatosis Type 1 (NF-1)	- **Lisch nodules**: Golden, bilateral nodules in the iris, appearing from teenage years.	Associated with axillary freckles (by age 10) and café-au-lait spots increasing in size/number in childhood.
Down Syndrome	- **Brushfield spots**: Small, white or greyish spots on the periphery of the iris.	Seen in individuals with Down syndrome.
Wilson's Disease	- **Kayser-Fleischer rings**: Copper deposition in Descemet's membrane of the cornea.	Pathognomonic for Wilson's disease; associated with liver and neurological symptoms.
Metabolic Disorders	- **Band keratopathy**: Calcium deposition in Bowman's layer of the cornea.	Requires evaluation of serum calcium and phosphate levels.
Marfan Syndrome	- **Ectopia lentis**: Lens dislocation, classically upwards.	Often associated with aortic regurgitation and systemic connective tissue abnormalities.
Homocystinuria	- **Inferior lens dislocation**: Downward displacement of the lens.	Associated with thromboembolic events and intellectual disability.
Endocarditis	- **Roth spots**: Retinal haemorrhages with pale centres.	Common in subacute bacterial endocarditis; also seen in leukaemia.
Leukaemia	- **Roth spots**: Retinal haemorrhages, sometimes with white centres.	Indicates hyperviscosity or infiltrative changes in the retina.
Sickle Cell Disease (SCD)	- **Black sunburst**: Chorioretinal scars, pathognomonic for SCD.	Retinal manifestations due to vaso-occlusion.

Hyphaema

Definition:

- Bleeding from iris vessels into the anterior chamber of the eye, potentially filling the chamber with blood.

Causes:

- **Trauma** (most common):
  - Blunt impact from small objects (e.g., champagne corks, squash balls, sports injuries).
- **Other Causes** (less common):
  - Neovascularisation, clotting disorders, or post-surgical complications.

Clinical Features:

- Visible blood in the anterior chamber (may range from mild to severe).
- Risk of **raised intraocular pressure (IOP)** in the acute stage.
- Decreased visual acuity.
- Pain and photophobia (if associated with high IOP).

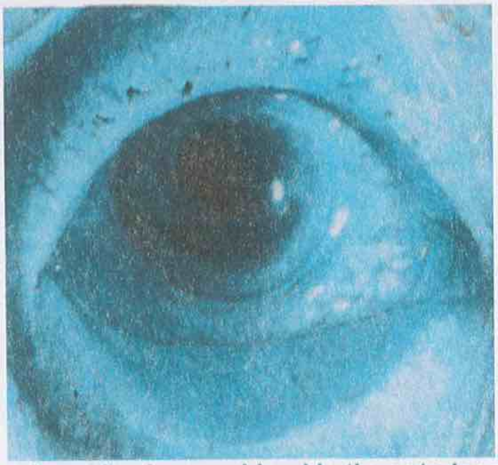
Complications:

- **Acute**:
  - Raised IOP due to obstruction of trabecular meshwork by blood clots.
  - Rebleeding (typically within 3–5 days).
- **Long-term**:
  - Corneal blood staining.
  - Vision loss from optic nerve damage or secondary glaucoma.

Management:

- **Conservative Management**:
  - **Strict bed rest** with head elevation at 30–45° to settle the blood.
  - Eye protection to prevent further trauma.
  - Avoid antiplatelets/anticoagulants if possible.
  - Avoid anticholinergic drops to stabilise the iris and minimise further bleeding risk.
- **Medical Therapy**:
  - **Intravenous carbonic anhydrase inhibitors** (e.g., acetazolamide) to reduce IOP.
  - **Avoid pupil-dilating drops** (e.g., anticholinergics) to keep the iris stable and reduce the risk of rebleeding.
  - Consider topical steroids to reduce inflammation.
- **Surgical Intervention**:
  - **Aspiration**:
    - Indicated in severe cases to prevent vision loss.
    - Necessary if blood clots persist or if IOP remains elevated despite medical treatment.

Intravenous carbonic anhydrase inhibitors is the most appropriate treatment



The slide shows hyphaema: blood in the anterior chamber.

4th edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Dermatology

Updated
2025

Skin Layers

Layer	Sub-Layers/Components	Description
Epidermis	**- Stratum corneum**	Outermost layer, composed of dead, flattened keratinocytes (corneocytes) providing a protective barrier.
	- Stratum lucidum	Found only in thick skin (palms, soles); translucent layer of keratinocytes.
	- Stratum granulosum	Contains keratohyalin granules, crucial for keratinization and water resistance.
	- Stratum spinosum	Provides strength and flexibility; contains desmosomes that connect keratinocytes.
	- Stratum basale (germinativum)	Basal layer; site of mitotic activity. Contains melanocytes, **keratinocytes**, and Merkel cells.
		Key Features: Avascular, depends on diffusion from the dermis.
Dermis	**- Papillary layer**	Upper layer composed of loose connective tissue; contains capillaries, lymphatics, and sensory neurons.
	- Reticular layer	Deeper layer of dense connective tissue; contains blood vessels, sweat glands, sebaceous glands, and hair follicles.
		Key Features: Provides strength, elasticity, and houses most skin appendages.
Hypodermis	- (Subcutaneous layer)	Composed of adipose tissue and connective tissue.
		Key Features: Provides insulation, cushioning, and energy storage.

Epidermis - 5 layers - bottom layer = stratum germinativum which gives rise to keratinocytes and contains melanocytes

Descriptive Terms for Skin Lesions

Term	Description
Plaque	Raised lesion greater than 1 cm in diameter.
Macule	Area of altered skin colour, irrespective of size.
Papule	Raised lesion less than 1 cm in diameter.
Ulcer	Discontinuity of the skin with complete loss of the epidermis and often portions of the dermis and subcutaneous fat.
Vesicle	Fluid-filled, well-circumscribed raised lesion.
Pustule	Small elevation of the skin containing cloudy or purulent material, usually consisting of necrotic inflammatory cells.
Bulla	Large vesicle containing serous fluid.
Fissure	Narrow but deep cracks in the skin.
Telangiectasia	Collection of enlarged capillaries visible on the skin or mucous membranes.
Lichenification	Epidermal thickening characterised by visible and palpable thickening of the skin with accentuation of skin markings.
Atrophy	Thinning of the skin due to loss of the epidermis, dermis, or subcutaneous tissue:
	- **Epidermal atrophy**: Skin appears thin and translucent.
	- **Dermal/Subcutaneous atrophy**: Leads to a depression in the skin.

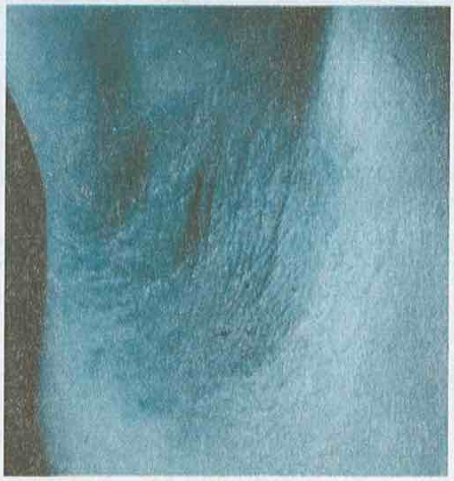
Acanthosis nigricans

Overview

- Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin
- presents as a dark **thickened** area of the skin of the back of the neck or the armpit,
- Obesity is the most common cause
- Classically acanthosis nigricans associated with malignancy appears abruptly, and it can precede diagnosis of malignancy.
- Diabetes causes acanthosis nigricans due to stimulation of insulin-like growth factor receptor-1.

Causes

- paraneoplastic phenomenon (usually tumours of the GI tract, especially adenocarcinoma of the stomach) **and** Endometrial carcinoma
- diabetes mellitus
- obesity
- polycystic ovarian syndrome
- acromegaly
- Cushing's disease
- hypothyroidism
- familial (autosomal dominant)
- Prader-Willi syndrome
- drugs: oral contraceptive pill, **nicotinic acid (Niacin)**



Management

- first line is treatment of the underlying cause.
- in persistent acanthosis nigricans despite treatment of the underlying cause, topical retinoids can be tried.

Acne rosacea

Definition:

- Chronic skin disease of unknown aetiology affecting the central face.

Features:

- **Affected Areas**:
  - Typically involves the nose, cheeks, and forehead.
- **Progression**:
  - Flushing is often the first symptom.
  - Telangiectasia (visible blood vessels) are common.
  - Persistent erythema develops later, with papules and pustules.
- **Complications**:
  - **Rhinophyma**: Thickened, bulbous appearance of the nose in advanced stages.
  - **Ocular Involvement**: Blepharitis, dry eyes, or irritation.

Management:

- **Topical Treatments**:
  - **Metronidazole**: For mild cases with limited papules and pustules.
- **Systemic Treatments**:
  - **Oxytetracycline**: For more severe disease with extensive lesions.
- **Supportive Measures**:
  - Recommend daily application of **high-factor sunscreen** to protect from triggers.
  - **Camouflage creams** to conceal redness.
- **Specialised Therapy**:
  - **Laser therapy**: Effective for prominent telangiectasia.

Acne rosacea treatment:

- mild/moderate: topical metronidazole
- severe/resistant: oral tetracycline

Acne Vulgaris

Definition:

- A disorder of the pilosebaceous follicles, characterised by obstruction with keratin plugs, resulting in comedones, inflammation, and pustules. Commonly affects the face, neck, and upper trunk.

Epidemiology:

- **Prevalence**: Affects 80–90% of teenagers.
- **Age**: Onset typically at 11–12 years; usually resolves by 20–30 years.
- **Gender**: More common in males during adolescence but more frequent in women in adulthood.
- **Acne beyond age 20**: Investigate for secondary causes.

Aetiology and Pathophysiology:

- **Hormonal Factors**:
  - Increased androgens during puberty → increased sebum production.
  - Menstrual cycle-related in women.

- **Follicular Hyperkeratosis**:
  - Keratin plug formation obstructs pilosebaceous follicles → comedones.
- **Bacterial Colonisation**:
  - *Cutibacterium acnes* induces inflammation → papules, pustules, nodules, cysts.
- **Drug-Induced**:
  - Anabolic steroids, corticosteroids, progestin-only contraceptives.

Features:

- **Primary Lesions**:
  - **Non-inflammatory**:
    - Closed comedones ("whiteheads").
    - Open comedones ("blackheads").
  - **Inflammatory**: Papules, pustules, nodules (>5 mm, often on the back and neck).
- **Secondary Lesions**: Hyperpigmentation, scarring.
- **Localisation**: Areas rich in sebaceous glands (face, shoulders, chest, back).

Complications:

- **Skin**:
  - Post-inflammatory hyperpigmentation.
  - Scarring (hypertrophic or atrophic).
  - Acne fulminans: Severe nodulo-cystic acne with systemic symptoms.
- **Psychological**:
  - Body dysmorphic disorder.
  - Emotional distress.

Classification of Severity:

- **Mild to Moderate Acne**:
  - Non-inflammatory lesions.
  - Up to 34 inflammatory lesions or 2 nodules.
- **Moderate to Severe Acne**:
  - ≥35 inflammatory lesions.
  - ≥3 nodules.

Management:

- **First-Line Treatment (12-week course)**:
  - **Mild to Moderate Acne**:
    - Topical benzoyl peroxide + clindamycin.
    - Topical adapalene + benzoyl peroxide.
  - **Moderate to Severe Acne**:
    - Topical adapalene + benzoyl peroxide + oral antibiotics (e.g., lymecycline or doxycycline).
    - Alternative oral antibiotics: Trimethoprim or macrolides (e.g., erythromycin).
  - **Pregnancy**:
    - Use oral erythromycin; avoid retinoids and tetracyclines.
  - **PCOS with Acne**:
    - Combined oral contraceptive pill (e.g., co-cyprindiol) may be added.
- **Second-Line Treatment**:
  - **Oral Isotretinoin**:
    - Indicated for severe, scarring acne unresponsive to standard therapies.
    - Consider oral prednisolone if initiating isotretinoin in acne fulminans.
  - **Photodynamic Therapy**:
    - For moderate to severe acne in adults if standard treatments fail.

- **Intralesional Corticosteroids**:
  - For severe inflammatory cysts.
- **Maintenance**:
  - Gradually reduce antibiotic use while continuing topical therapy.
- **Acne-Related Scarring**:
  - Refer for CO_2 laser treatment or glycolic acid peel if scarring persists after 1 year.

Side Effects:

- **Topical Treatments**:
  - Skin irritation: Start with alternate-day or short-contact application.
- **Antibiotics**:
  - Risk of antimicrobial resistance.
  - Gram-negative folliculitis: Treat with high-dose trimethoprim if it occurs.
- **Oral Isotretinoin**:
  - Teratogenicity; requires strict contraception.

Weight loss is the most important intervention.

Isotretinoin

Overview:

- Oral retinoid used for the treatment of **moderate to severe acne.**
- Two-thirds of patients experience long-term remission or cure after a course.

Indications:

- **Moderate to severe acne**, particularly cases resistant to standard therapies.

Contraindications:

- **Pregnancy**: Strong teratogenic effects.
- **Liver disease.**
- Women of childbearing age **without effective contraception.**

Precautions:

- **Pregnancy Testing**: Mandatory serum/urine pregnancy test before initiation in females of childbearing potential.
- **Contraception**:
  - Ideally use two forms (e.g., combined oral contraceptive and condoms).
  - Discontinue isotretinoin at least one month before attempting pregnancy.

Side Effects:

- **Common**:
  - **Dry skin, eyes, and lips**: **Most frequent side effect.**
  - **Nosebleeds**: Due to nasal mucosa dryness.
  - **Photosensitivity**.
- **Psychological**:
  - **Low mood** or depression (monitor mental health).
- **Systemic**:
  - **Raised triglycerides.**
  - **Hair thinning.**
  - **Benign intracranial hypertension**: Avoid concomitant tetracycline use.
- **Laboratory Abnormalities**:
  - ↑ Triglycerides, ↓ HDL, ↑ Glucose.

Retinoid (isotretinoin) therapy should be discontinued at the latest one month

Alopecia

Definition:

- **Alopecia** refers to hair loss, which can be partial or complete, and it may affect the scalp or other parts of the body.

Types of Alopecia:

1. **Non-Scarring Alopecia**:
    - Hair follicles are intact, and regrowth is possible.
    - Includes:
        - **Androgenetic Alopecia** (Male and Female Pattern Hair Loss):
            - Progressive thinning of hair due to genetic and hormonal factors.
            - Men: Receding hairline and vertex balding.
            - Women: Diffuse thinning over the crown.
        - **Alopecia Areata**:
            - Autoimmune disorder causing patchy, non-scarring hair loss.
            - Associated with nail pitting and other autoimmune diseases.
        - **Telogen Effluvium**:
            - Diffuse hair shedding triggered by stress, illness, or hormonal changes.
            - Hair enters the telogen (resting) phase prematurely.
        - **Trichotillomania**:
            - Hair loss due to compulsive hair pulling.
2. **Scarring (Cicatricial) Alopecia**:
    - Hair follicles are destroyed, leading to permanent hair loss.
    - Includes:
        - **Lichen Planopilaris**:
            - Inflammatory condition with perifollicular erythema and scaling.
        - **Discoid Lupus Erythematosus**:
            - Associated with scaly plaques and scarring.
        - **Central Centrifugal Cicatricial Alopecia**:
            - Gradual hair loss starting at the vertex, common in African descent.

Clinical Features:

- **Non-scarring Alopecia**:
    - Hair thinning or patchy hair loss without signs of inflammation or scarring.
- **Scarring Alopecia**:
    - Loss of follicular openings.
    - Inflammatory signs: redness, scaling, pustules.
    - Permanent hair loss.

Alopecia Areata

Definition:

- Presumed autoimmune condition causing **localised, well-demarcated patches of non-scarring hair loss**.

Features:

- Localised patches of non-scarring hair loss.
- Remaining hairs have an **'exclamation mark' appearance**:
    - Tapered towards the base, with small, broken hairs at the edges.
- Severe forms:
    - **Alopecia Totalis**: Total loss of scalp hair.
    - **Alopecia Universalis**: Total loss of all body hair.

Treatment:

- **General Approach**:
  - Hair regrows in **50% of cases within 1 year** and in **80–90% eventually**.
  - Reassurance and explanation are sufficient for many patients.
- **Specific Treatments**:
  - **Intralesional corticosteroids**: First-line for localised hair loss (e.g., intralesional triamcinolone).
  - **Topical corticosteroids**.
  - **Topical minoxidil**.
  - **Contact immunotherapy**: Induces an allergic response to promote hair regrowth.
  - **Phototherapy**.
  - **Dithranol**.
  - **Wigs**: For extensive hair loss.

Differential Diagnosis:

- **Androgenetic Alopecia**:
  - Gradual, diffuse hair loss post-puberty.
  - Males: Loss over temporal regions and vertex.
- **Discoid Lupus Erythematosus (DLE)**:
  - Scarring alopecia with atrophic patches and visible follicular loss.
  - May have other DLE lesions; irreversible if untreated.
- **Telogen Effluvium**:
  - Diffuse hair shedding 1–3 months after a stressful event (e.g., surgery, childbirth).
  - Hair loss is never complete and regrowth is usually complete within 3–5 months.
- **Trichotillomania**:
  - Localised hair loss in **bizarre patterns**.
  - **Hairs of differing lengths** within and at the edges of patches.
  - Often associated with a history of hair-pulling, more common in children.

Pemphigus vulgaris

Definition:

- Autoimmune disease caused by **IgG antibodies** directed against **desmoglein 3**, a cadherin-type epithelial cell adhesion molecule, leading to **acantholysis** (loss of cell-to-cell adhesion).

Epidemiology:

- More common in the **Ashkenazi Jewish population**.
- Predominantly affects individuals aged **50–60 years** but can occur at any age.

Features:

- **Mucosal Involvement**:
  - Common presenting symptom.
  - **Oral ulceration** occurs in 50–70% of patients.
- **Skin Blistering**:
  - **Flaccid, thin-walled vesicles and bullae** that rupture easily (intact blisters are rare).
  - Painful but not itchy.
  - Lesions may appear **months after mucosal symptoms**.
- **Nikolsky's Sign**:
  - Positive: Bullae spread with tangential pressure applied to the skin.

- **Histology and Immunofluorescence**:
  - **Acantholysis**: Separation of keratinocytes.
  - **Direct immunofluorescence**: IgG deposition in a "chicken wire" pattern along keratinocyte membranes.
  - Biopsy reveals **deposition of IgG** on keratinocyte desmosomes.

Management:

- **First-Line Therapy**:
  - **Systemic corticosteroids** to control inflammation and prevent new blister formation.
- **Immunosuppressants**:
  - Examples: Azathioprine, mycophenolate mofetil, or rituximab.

Blisters/bullae
- no mucosal involvement: bullous pemphigoid
- mucosal involvement: pemphigus vulgaris

Pemphigus vulgaris
- **Caused by antibodies (IgG) directed against desmoglein 3, a cadherin-type epithelial cell adhesion molecule.**
- **mucosal ulceration is common and often the presenting symptom. Oral involvement is seen in 50-70% of patients**

Mucosal ulceration is common with pemphigus

Bullous pemphigoid

Overview

- Autoimmune blistering disease that most commonly affects older adults
- Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin.
- This is secondary to the development of **antibodies against hemidesmosomal proteins BP180 and BP230**
  - ⇨ caused by (IgG) autoantibodies against components of the basement membrane.

Epidemiology

- Pemphigoid, erythema multiforme, and herpes are the commonest causes of a blistering rash.
- Bullous pemphigoid is more common in elderly patients (over 60 years).
  - ⇨ **Remember, this is a disease of the elderly (uncommon under the age of 60).**

Features

- Include
- itchy, tense blisters typically around flexures
- the blisters usually heal without scarring
- mouth is usually spared*
  - ⇨ *in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.

Investigations

- **Perilesional skin biopsy for examination by direct immunofluorescence** shows IgG and C3 at the dermo-epidermal junction

Differential diagnosis

- Blistering in pemphigoid occurs at the sub-epidermal level - deeper than the blisters of pemphigus vulgaris (which occur at the dermal-epidermal junction); hence the tense blisters seen in pemphigoid. Blisters are thin-walled and fragile in pemphigus - few intact blisters are ever seen.
  - ⇨ In pemphigus vulgaris, mucous membrane involvement is more common, and intact bullae are rare. Skin biopsy for routine and direct immunofluorescence is needed to differentiate from bullous pemphigoid.

Management

- Topical corticosteroids: 1st line for all patient who can tolerate topical therapy
- Doxycycline: 1st line for **patients with mild disease who cannot tolerate topical therapy**
- Oral corticosteroids: 1st line for **patients with extensive disease who cannot tolerate topical therapy**
  - ⇨

	Pemphigus vulgaris	Bullous pemphigoid
Appearance		
Age	Younger	Older
Mucous membrane involvement	Yes	Rare
Autoantibodies	Against desmoglein 3	Against hemidesmosomes
Blister location	Intraepidermal (superficial)	Subepidermal (deep)
Blister quality	Flaccid, rupture easily	Tense and firm
Nikolsky's sign	Nikolsky positive	Nikolsky negative
Prognosis	Poor	Favorable

Dermatitis herpetiformis (DH)

Dermatitis herpetiformis is associated with HLA-DR3

Dermatitis herpetiformis - caused by IgA deposition in the dermis

Overview

- autoimmune blistering skin disorder **associated with coeliac disease** and gluten sensitivity.
- caused by deposition of IgA in the dermis.
- associated with HLA-DR3.
- Virtually all patients with DH carry the HLA DQ2 or HLA DQ8 haplotype.

Features

- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

Association

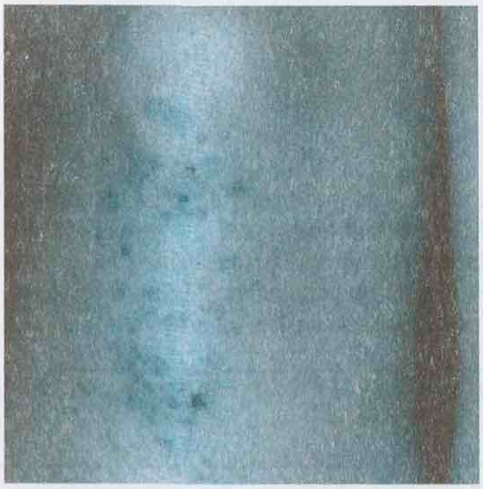
- increased risk for the development of other autoimmune diseases.
  - ⇨ Thyroid disease is the most common autoimmune disorder associated with DH.
- increased risk for lymphoma.

Diagnosis

- skin biopsy: direct immunofluorescence (The gold standard test for diagnosis) shows:
  - ⇨ Subepidermal **deposition of IgA**
    - in a **granular pattern** in the upper **dermis** (in the **dermal papillae**)(Granular IgA deposits at the basement membrane zone)
  - ⇨ neutrophilic dermal infiltrates in the superficial dermis
    - Neutrophils are the immune cell that is involved in the blistering skin lesion DH.
- Serology
  - ⇨ blood test showing the presence of IgA antibodies against tissue transglutaminase.

Management

- gluten-free diet
- dapsone



Dermatitis herpetiformis

Discoid lupus erythematous

Pathology

- it is a chronic type of Cutaneous lupus erythematosus (CLE)
- **characterised by follicular keratin plugs**
- characterised by a well-demarcated macular rash with erythema, scales, and plaques that often results in scarring and atrophy.

Aetiology

- thought to be **autoimmune** in aetiology

Association

- may occur in the absence or in association with systemic SLE.
  - ⇨ Approximately 10% of patients may have signs of SLE.

Epidemiology

- generally seen in younger females.
- occurs 2-3 times more frequently in women than in men
- more common in African–Caribbean female.

Features

- erythematous, raised rash, sometimes scaly
- may be photosensitive
- more common on face, neck, ears and scalp
- lesions heal with atrophy, scarring (may cause scarring alopecia), and pigmentation

Diagnosis

- made by biopsy of the lesion.

Management

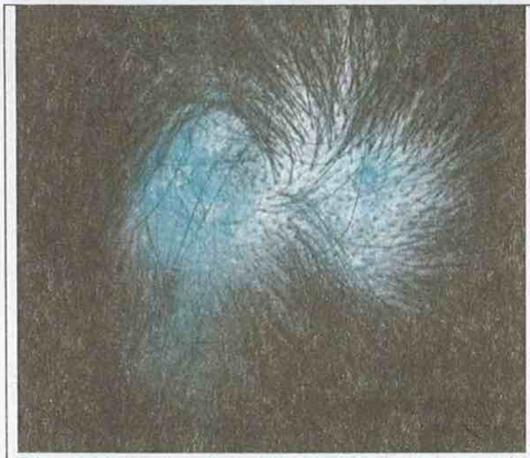
> Discoid lupus erythematous - topical steroids → oral hydroxychloroquine

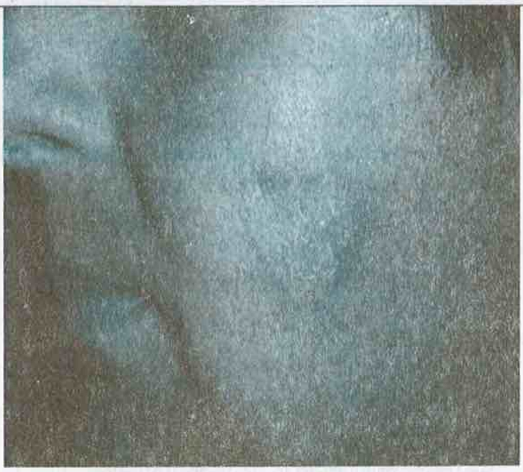
- **1st line**: topical potent steroid cream
- **2nd line**: oral antimalarials e.g. hydroxychloroquine
  - ⇨ other options
    - Topical calcineurin inhibitors
    - Intralesional corticosteroids
    - Oral corticosteroids.
- Avoid sun exposure

Prognosis

- **The risk of progression to SLE** in patients with DLE was demonstrated to be higher than previously reported (**16.7% progression within 3 years of diagnosis,** as compared with previous data indicating that <5-10% of patients with DLE progress to SLE).
- **children** with DLE seem to have a higher early rate of progression to SLE (up to **25%**) indicating that the **age at onset might influence disease severity**

> **According to a recent epidemiologic study, approximately 16% of patients with discoid lupus erythematosus (DLE) may develop systemic involvement within 3 years of diagnosis.**


Discoid lupus erythematous affecting the scalp


Discoid lupus erythematous affecting the face

Contact dermatitis

Definition:

- Inflammatory skin reaction caused by contact with an irritant or allergen.

Types

Feature	Irritant Contact Dermatitis (ICD)	Allergic Contact Dermatitis (ACD)
Pathophysiology	Direct damage to the skin barrier by irritants (non-immunologic).	Type IV hypersensitivity reaction mediated by T-cells (immunologic).
Onset	Occurs quickly after exposure (minutes to hours).	Delayed onset (hours to days after exposure).
Triggers	Soaps, detergents, solvents, acids, alkalis, friction, repeated wetting or drying.	Allergens such as nickel, fragrances, rubber, preservatives, plants (e.g., poison ivy).
Symptoms	Burning, stinging, or dryness.	Intense itching, swelling, and redness.
Lesions	- Erythema, dryness, scaling. - Chronic cases: fissures, lichenification.	- Erythema, edema, vesicles, or bullae. - Chronic cases: lichenification and scaling.
Location	Confined to the area of contact with the irritant.	Often spreads beyond the area of contact.
Common Sites	Hands, face (especially in occupational exposure).	Any site in contact with the allergen (e.g., wrists for nickel, neck for fragrances).
Diagnosis	Clinical history and examination. No immunologic testing required.	Patch testing confirms the allergen responsible.
Management	- Avoid irritants. - Use emollients to repair the skin barrier. - Topical corticosteroids for inflammation.	- Avoid allergens. - Topical corticosteroids for inflammation. - Oral corticosteroids for severe cases.
Prognosis	Symptoms resolve when exposure ceases and the skin barrier is restored.	Symptoms persist until the allergen is avoided and inflammation is treated.

The main difference between allergic contact dermatitis and irritant contact dermatitis:

- The rash caused by **allergic contact dermatitis** confined to contacted area, whereas in **irritant contact dermatitis**, the rash is more widespread.
- In **allergic contact dermatitis** the rash usually appears after a day or two after exposure to the allergen, unlike **irritant contact dermatitis** that appears immediately after the contact with the trigger.

Pruritus

The main characteristics of the most important causes of pruritus

Cause	Key Characteristics
Liver Disease	- History of alcohol excess. - Stigmata of chronic liver disease: spider naevi, bruising, palmar erythema, gynaecomastia. - Evidence of decompensation: ascites, jaundice, encephalopathy.
Iron Deficiency Anaemia	- Pallor. - Other signs: koilonychia (spoon-shaped nails), atrophic glossitis, post-cricoid webs, angular stomatitis.
Polycythaemia	- Pruritus, particularly after warm baths. - 'Ruddy complexion'. - Associated with gout and peptic ulcer disease.
Chronic Kidney Disease	- Lethargy, pallor. - Oedema and weight gain. - Hypertension.
Lymphoma	- Night sweats. - Lymphadenopathy. - Splenomegaly, hepatomegaly. - Fatigue.
Other Causes	- **Endocrine**: Hyperthyroidism, hypothyroidism, diabetes.
	- **Pregnancy-related pruritus**.
	- **Senile pruritus**: Itching in the elderly without a clear cause.
	- **Skin disorders**: Eczema, scabies, psoriasis, pityriasis rosea.
	- **Idiopathic Urticaria**: Up to 50% of cases have no identifiable cause.

Eczema herpeticum

- Eczema herpeticum describes a severe primary infection of the skin by herpes simplex virus 1 or 2.

Features

- It is more commonly seen in children with atopic eczema.
- **Typically, the child has a high fever for seven days,** and recurrent attacks can occur.
- It may affect any site but is most often seen on face and neck.

Treatment

- Eczema herpeticum is considered as one of the few dermatological emergencies.
- As it is potentially life threatening children should be admitted for IV acyclovir

Complications

- Death can result from physiological disturbances (loss of fluid electrolytes and protein through the skin) or dissemination of the virus to brain and other organs or from secondary bacterial sepsis.
- may be further complicated by secondary staphylococcal infection. This is treated by adding oral antibiotics, for example, flucloxacillin 500 mg q.i.d.

Eczema: topical steroids

Topical steroids
- moderate: Clobetasone butyrate 0.05%
- potent: Betamethasone valerate 0.1%
- very potent: Clobetasol propionate 0.05%

Use weakest steroid cream which controls patients symptoms

The table below shows topical steroids by potency

Mild	Moderate	Potent	Very potent
Hydrocortisone 0.5-2.5%	Betamethasone valerate 0.025% (Betnovate RD) Clobetasone butyrate 0.05% (Eumovate)	Fluticasone propionate 0.05% (Cutivate) Betamethasone valerate 0.1% (Betnovate)	Clobetasol propionate 0.05% (Dermovate)

Finger tip rule
- 1 finger tip unit (FTU) = 0.5 g, sufficient to treat a skin area about twice that of the flat of an adult hand

Topical steroid doses for eczema in adults

Area of skin	Fingertip units per dose
Hand and fingers (front and back)	1.0
A foot (all over)	2.0
Front of chest and abdomen	7.0
Back and buttocks	7.0
Face and neck	2.5
An entire arm and hand	4.0
An entire leg and foot	8.0

The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

Area	Amount
Face and neck	15 to 30 g
Both hands	15 to 30 g
Scalp	15 to 30 g
Both arms	30 to 60 g
Both legs	100 g
Trunk	100 g
Groin and genitalia	15 to 30 g

Pompholyx

Definition

- Pompholyx is a type of eczema which affects both the hands (cheiropompholyx) and the feet (pedopompholyx). It is also known as dyshidrotic eczema

Features

- small blisters on the palms and soles
- pruritic, sometimes burning sensation
- once blisters burst skin may become dry and crack

Management

- cool compresses
- emollients
- topical steroids

Erythema ab igne

Definition

- A skin condition caused by prolonged exposure to infrared radiation, leading to localised erythematous and hyperpigmented patches.

Pathophysiology

- Chronic exposure to heat causes damage to the dermal elastic fibres.
- This results in a reticulated pattern of erythema, telangiectasia, and subsequent hyperpigmentation.

Clinical Features

- **Location:** Classically presents on the front of the legs.
- **Appearance:**
  - Reticulated (net-like) erythematous patches.
  - Hyperpigmentation and telangiectasia.
- **Typical History:**
  - An elderly individual frequently sitting close to a fire or heater.
  - May also occur from chronic use of a hot water bottle.

Associated Conditions

- **Hypothyroidism:** Patients often feel cold and are more likely to sit near heaters or fires, increasing the risk.

Complications

- If the cause is not removed, **squamous cell carcinoma** (SCC) may develop in the affected area.

Management

1. **Primary Management:**
   - Remove the heat source to prevent further damage.
2. **Secondary Management:**
   - Monitor for malignant changes in the affected area.
   - Consider biopsy if there are suspicious lesions (e.g., non-healing ulcers, induration).

Key Points

- Erythema ab igne is caused by repeated exposure to infrared radiation.
- It presents as reticulated, erythematous patches with hyperpigmentation.
- Associated with hypothyroidism due to increased cold sensitivity.
- Chronic cases may lead to **squamous cell carcinoma** if untreated.

> - Hypothyroidism can make patients feel cold and hence more likely to sit next a heater / fire.
> - **If the cause is not treated then patients may go on to develop** squamous cell skin cancer.

Erythema ab igne

Erythema ab igne

Erythema multiforme

Pathophysiology

- Type IV hypersensitivity reaction; triggered by the following
  - ⇨ Infections: herpes simplex virus (HSV - the most common cause), Mycoplasma pneumoniae.
  - ⇨ Drugs: phenytoin; beta-lactam antibiotics (e.g., penicillins); sulfonamides

Classification

- **Erythema multiforme minor** (typical targets or raised oedematous papules, with acral distribution, without involvement of mucosal sites, and involving <10% total body surface area)
- **Erythema multiforme major** (typical targets or raised oedematous papules, with acral distribution, plus involvement of 1 or more mucosal sites, and involving <10% total body surface area)

Features

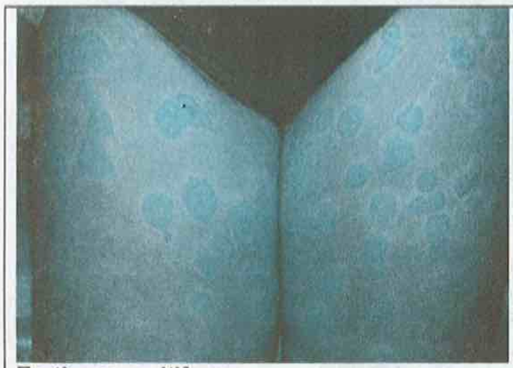
- Erythematous , maculopapular rash (many forms), hence the 'multiforme' in the name.
- **Target lesions** (also called iris lesion): an inner dark red/brown zone, surrounded by a pale zone, and an outer erythematous ring.
- Distribution: Symmetrical and affects backs of hands and feet first → spreads proximally and can affect the entire body.

Treatment

- Supportive: treat the underlying infection or stop the offending drug .

Prognosis

- usually mild and self-limiting disease with the lesions healing within 2 to 3 weeks without scarring.


Erythema multiforme

Erythema multiforme

Differential diagnosis

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the same entity but differ in terms of disease severity (based on surface area of skin involved).
  - ⇨ < 10% – SJS
  - ⇨ 10–30% – SJS/TEN overlap
  - ⇨ 30% – Toxic epidermal necrolysis (severe SJS)

Erythema multiforme VS Stevens-Johnson syndrome

	Erythema multiforme (EM)	Stevens-Johnson syndrome (SJS)
Causes	usually triggered by infections, most commonly herpes simplex virus (HSV). Medications are uncommon cause (<10%)	Most commonly triggered by drugs (~ 80%).
Lesions distribution	Lesions begin on the extremities	Lesions typically begin on the face and trunk.
Target lesions	Typical target lesions	No typical target lesions.
Mucosal membranes	Mucosal membranes may be involved, but usually not	Mucosal membranes almost always involved
Swelling	No associated swelling of face, hands or feet	Associated swelling of face, hands or feet
Systemic symptoms	Systemic symptoms such as fever and malaise, are absent or mild	Systemic symptoms such as fever and malaise, are prominent
Histology	high density of cell infiltrate rich in T-lymphocytes. (more dermal inflammation and individual keratinocyte necrosis)	poor infiltrate of macrophages and dendrocytes with tumor necrosis factor (TNF) (minimal inflammation and sheets of epidermal necrosis.)
Severity	Usually mild	Shock may develop
Treatment	Treat underline cause	need urgent supportive care , fluid resuscitation similar to that of burns and Wound management
Prognosis	Self-limiting	High mortality rate (SJS: ~ 25%, TEN: ~ 50%)

Erythema multiforme (EM):
- **a type IV hypersensitivity reaction of the skin.**
- **can be triggered by certain infections (e.g., HSV, Mycoplasma pneumonia) and medications (e.g., beta-lactam antibiotics, sulfonamides, phenytoin).**

Erythema multiforme (EM):
- **EM is characterized by lesions of varying morphology (e.g., macules, papules, vesicles) that typically progress to target lesions and spread proximally from the backs of the hands and feet.**

***Herpes simplex* virus (HSV) infection is the commonest cause of Erythema multiforme**

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Definition

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions, most commonly triggered by medications, characterized by extensive necrosis and detachment of the epidermis
- SJS and TEN are the same entity but differ in terms of disease severity (based on surface area of skin involved).
  - ⇨ < 10% – SJS
  - ⇨ 10–30% – SJS/TEN overlap
  - ⇨ ≥ 30% – Toxic epidermal necrolysis (severe SJS)

Pathophysiology

- Delayed hypersensitivity reaction (type IV)

Causes

- Most commonly triggered by medications, ~ 80% of cases
  - ⇨ Antibiotics: sulfonamides (e.g., TMP/SMX), aminopenicillins
  - ⇨ Antiepileptics: phenytoin, phenobarbital, lamotrigine, valproic acid, carbamazepine,
  - ⇨ Sulfasalazine
  - ⇨ Nonsteroidal anti-inflammatory drugs (NSAIDs)

Features

- Begins with a prodrome of fever and influenza-like symptoms one to three days before the development of mucocutaneous and skin lesions.
- Extensive, full-thickness epidermal necrosis and sloughing (resembling large superficial burns)
- Mucosal membranes: almost always involved ~ 90% of cases
- Systemically unwell e.g. pyrexia, tachycardic, shock may develop
- Positive Nikolsky's sign (the epidermis separates with mild lateral pressure)
- Skin biopsy
  - ⇨ Keratinocyte necrosis with apparent subepidermal split
  - ⇨ Eosinophilic infiltration with minimal infiltration of lymphocytes and histiocytes around blood vessels

Treatment

- Stop precipitating factor **is most likely to improve prognosis**
- Supportive care, often in intensive care unit
- Wound management: similar to that of burns

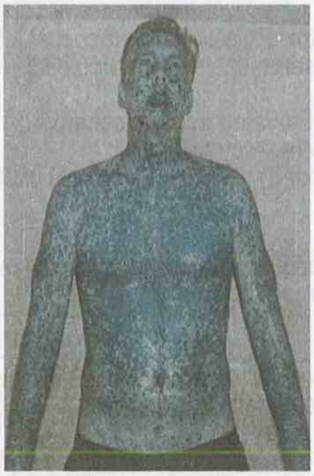
Comparison: Stevens-Johnson Syndrome (SJS) vs. Toxic Epidermal Necrolysis (TEN)

Feature	Stevens-Johnson Syndrome (SJS)	Toxic Epidermal Necrolysis (TEN)
Definition	Severe mucocutaneous reaction with <10% of body surface area (BSA) involved.	Severe mucocutaneous reaction with ≥30% BSA involved.
Severity	Milder end of the disease spectrum.	Most severe form with high mortality.
Skin Involvement	Limited to <10% of BSA.	Extensive, involving ≥30% of BSA.
Overlap Category	SJS only.	Includes SJS/TEN overlap (10–30% BSA).
Onset	1–3 days after prodromal symptoms.	Similar to SJS but lesions progress more rapidly.
Mortality Rate	~5–10%.	~30–50%.
Triggers	Medications (same triggers for both).	Medications (same triggers for both).
Systemic Involvement	Moderate systemic effects (e.g., fever, tachycardia).	Severe systemic effects (e.g., shock, organ failure).
Treatment	Stop causative agent, supportive care, wound management.	Same as SJS, but intensive care required.
Prognostic Scoring	SCORTEN score (same for both).	SCORTEN score (same for both).

Key Differences

- **Surface Area**: SJS involves <10% BSA; TEN involves ≥30% BSA.
- **Mortality**: Higher in TEN due to extensive skin loss and systemic complications.
- **Severity**: TEN is considered a life-threatening condition requiring specialised burn unit or ICU care.

Shared Features: Both conditions are caused by medications, involve epidermal necrosis, present with mucosal lesions, and require supportive care as the cornerstone of treatment.



Stevens-Johnson syndrome (SJS)

Erythema Nodosum (EN)

Definition

- Erythema nodosum (EN) is an inflammatory panniculitis (inflammation of subcutaneous fat), characterized by tender, red nodules, typically located on the anterior shins.

Pathophysiology

- EN is a delayed hypersensitivity reaction (Type IV) to a variety of antigens, leading to inflammation in the subcutaneous fat.

Causes

1. **Infectious**:
    - **Bacterial**: Streptococcal infections, tuberculosis, Yersinia, Brucella.
    - **Fungal**: Histoplasmosis, coccidioidomycosis.
    - **Viral**: Epstein-Barr virus (EBV), hepatitis B/C, HIV.
2. **Non-infectious**:
    - **Autoimmune diseases**: Sarcoidosis, inflammatory bowel disease (Crohn's disease, ulcerative colitis).
    - **Medications**: Sulfonamides, oral contraceptives, penicillin, NSAIDs.
    - **Malignancy**: Rarely associated.
3. **Idiopathic**:
    - Up to 55% of cases have no identifiable cause.

Clinical Features

- **Lesions**:
    - Painful, erythematous, warm, and tender nodules.
    - Commonly located on the anterior shins but may also appear on arms or thighs.
    - Nodules do not ulcerate.
- **Systemic Symptoms**:
    - Fever, malaise, arthralgia, and fatigue.
- **Course**:
    - Typically self-limiting, resolving in 2–6 weeks with or without treatment.
    - Lesions fade to bruise-like discolouration as they resolve.

Diagnostic Investigations

- **Clinical Diagnosis**:
    - Based on characteristic nodules.
- **Supportive Investigations**:
    - Throat swab or ASO titre: Rule out streptococcal infection.
    - Chest X-ray: Rule out sarcoidosis or tuberculosis.
    - Blood tests:
        - ESR and CRP: Elevated in most cases.
        - CBC: May show leukocytosis.
    - Skin biopsy (rarely needed): Septal panniculitis without vasculitis.

Treatment

1. **Underlying Cause**:
    - Treat infections (e.g., antibiotics for streptococcal pharyngitis).
    - Discontinue triggering medications.
2. **Symptomatic Management**:
    - Rest and leg elevation.
    - NSAIDs (e.g., ibuprofen 200–400 mg every 6–8 hours) for pain and inflammation.
    - Potassium iodide: Occasionally used for refractory cases.
3. **Severe Cases**:
    - Corticosteroids (e.g., prednisone 0.5–1 mg/kg daily) only if infection is excluded.

Key Points for MRCP

- EN is commonly associated with **streptococcal infections**, **sarcoidosis**, and **inflammatory bowel disease**.
- Lesions are **non-ulcerative** and self-resolving **within 6 weeks. lesions heal without scarring.**
- Treat the **underlying cause** and manage symptoms with **NSAIDs**.
- **Biopsy** is rarely needed unless the diagnosis is uncertain.

Always do a chest x-ray on a patient with erythema nodosum, to exclude sarcoidosis

Erythema Induratum (EI)

Definition

- Chronic nodular vasculitis, typically affecting the posterior calves, associated with **Mycobacterium tuberculosis (MTB)**.

Pathophysiology

- Hypersensitivity reaction (Type IV) to **MTB antigens**.

Causes

- **Tuberculosis** (most common association).
- Rarely non-tuberculous infections or idiopathic.

Clinical Features

- Painful, **tender nodules** on the posterior lower legs.
- Nodules may ulcerate and heal with scarring.
- Recurrence is common.

Diagnosis

- Clinical features + history of tuberculosis.
- **Skin biopsy**: Lobular panniculitis with granulomas and caseous necrosis.
- **Tuberculin skin test**: Often positive.

Treatment

- **Anti-tubercular therapy (ATT)**: Primary treatment if associated with MTB.
- Supportive care for symptoms.

Key Points

- Strongly linked to **TB**.
- Nodules often ulcerate and scar.
- Treat with **ATT** for resolution.

Erythema Induratum (EI)

- chronic, recurrent, tender, subcutaneous, and sometimes ulcerated nodules on the lower legs that may also appear elsewhere
- Females are more frequently affected.
- It is found in association with tuberculosis.
- **Erythema nodosum also commonly associated with TB but do not ulcerate**

Erythrasma

- Erythrasma is a generally asymptomatic, flat, slightly scaly, pink or brown rash usually found in the groin or axillae.
- It is caused by an overgrowth of the diphtheroid Corynebacterium minutissimum
- Examination with Wood's light reveals a coral-red fluorescence.
- Topical miconazole or antibacterial are usually effective. Oral erythromycin may be used for more extensive infection

Erythroderma

Definition

- Widespread redness and scaling affecting >90% of body surface area.

Causes

1. **Dermatological**: Eczema (40%), psoriasis (25%), pityriasis rubra pilaris.
2. **Drug-induced**: Sulphonamides, NSAIDs, anticonvulsants, etc.
3. **Systemic diseases**: Cutaneous T-cell lymphoma, leukaemia.
4. **Idiopathic**: No identifiable cause in some cases.

Mechanism

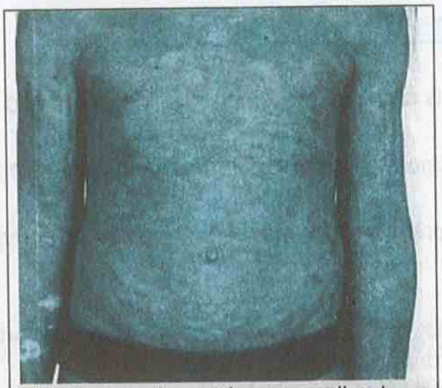
- **Cutaneous thermal dysregulation**:
  - Increased blood flow → Heat and fluid loss.
  - Accelerated skin turnover → Skin sloughing.

Clinical Features

- Extensive erythema with scaling (appears 2–6 days later).
- **Systemic symptoms**: Fever, shivering, malaise.
- Complications: Fluid/electrolyte imbalance, secondary infections, hypothermia.

Management

- **Supportive care**:
  - Emollients (e.g., hydromol) every 2–4 hours.
  - Warm environment to prevent heat loss.
  - Stop non-essential medications.
- **Hospital admission** for severe cases.
- Treat underlying cause (e.g., antibiotics for infections, steroids cautiously).



This image shows the generalised erythematous rash seen in patients with erythroderma, sometimes referred to as 'red man syndrome'

Onycholysis

Definition

- Separation of the nail plate from the nail bed, starting at the distal or lateral edge.

Causes

1. **Trauma**: Repeated nail injury or pressure.
2. **Infections**: Fungal (onychomycosis), bacterial (Pseudomonas).
3. **Dermatological Conditions**: Psoriasis, lichen planus, eczema.
4. **Systemic Diseases**: Hyperthyroidism, iron deficiency, diabetes.
5. **Medications**: Tetracyclines, retinoids, chemotherapy agents.
6. **Other**: Allergic reactions (nail products), prolonged water exposure.

Clinical Features

- Detachment of the nail plate from the nail bed.
- Nail may appear white, yellow, or green (secondary infection).
- No pain unless secondary infection is present.

Diagnosis

- **Clinical examination**: Characteristic nail changes.
- **Investigations** (if needed):
  - Fungal culture or nail clippings for microscopy.
  - Blood tests (if systemic disease is suspected).

Treatment

- **Treat Underlying Cause**:
  - Antifungals for fungal infections (e.g., terbinafine).
  - Topical steroids for psoriasis or eczema.
  - Manage systemic diseases (e.g., hyperthyroidism).

Fungal Nail Infections (Onychomycosis)

Definition:

- Fungal infection of nails causing thickening, discoloration, and brittleness.

Causes:

- *Trichophyton rubrum* (most common), *Candida*, and non-dermatophyte moulds.

Risk Factors:

- Diabetes, immunosuppression, trauma, tight footwear, poor hygiene.

Clinical Features

- **Nail Changes**:
  - Thickened, brittle, discoloured nails (white, yellow, or brown).
  - Subungual debris and crumbling edges.
  - Nail distortion and lifting (onycholysis).
- **Types**:
  - **Distal lateral subungual**: Starts at the nail edge (most common).
  - **White superficial**: Powdery white patches on the nail surface.
  - **Proximal subungual**: Starts at the base, common in immunosuppressed.
  - **Candida onychomycosis**: Thickened, discoloured fingernails often with paronychia.

Diagnosis

- Nail clippings/scrapings for microscopy, culture, or PCR.

Treatment

- **Oral Antifungals**:
  - first-line: oral terbinafine
  - alternative: oral itraconazole.
  - Treatment duration:
    - for fingernail infections 6 weeks - 3 months
    - for toenails 3 - 6 months
  - Monitor liver function for hepatotoxicity.

Note: Confirm diagnosis before systemic therapy.

Onychomycosis

- **Wood's lamp**
  - ⇨ **useful, rapid and easy way to confirm the diagnosis**
  - ⇨ Yellow to yellow-green fluorescence is characteristic of fine scales taken from active fungal lesions

Dermatophyte nail infections - use oral terbinafine

***Candida* infection: mild disease should be treated with topical antifungals (e.g. Amorolfine) whilst more severe infections should be treated with oral itraconazole for a period of 12 weeks**

Beau's lines

Nail conditions

- **Fungal nail infections present with thickening and discolouration of the nail plate with prominent subungual debris. It usually only affects one or several nails.**
- **Nail psoriasis presents with pitting, onycholysis, subungual debris and yellowish nail discolouration.**
- **Beau's lines is a benign nail condition that presents as a jagged transverse groove on the nail plate corresponding to an episode of nail growth arrest, which can occur during an episode of severe medical illness. It usually affects several nails.**

Granuloma annulare

Definition

- Benign, self-limiting skin condition with smooth, annular (ring-shaped) lesions, typically on extremities.

Causes & Associations

- **Idiopathic** (most common).
- Linked to **diabetes**, thyroid disease, and HIV.

Clinical Features

1. **Localized**: Skin-coloured or erythematous annular plaques on hands, feet, elbows, knees.
2. **Generalized**: Widespread symmetrical lesions on the trunk and extremities.
3. **Subcutaneous**: Firm nodules under the skin (common in children).
4. **Perforating**: Lesions with central crust or ulceration.

Diagnosis

- Clinical diagnosis; **skin biopsy** if unclear (shows necrobiotic granulomas).

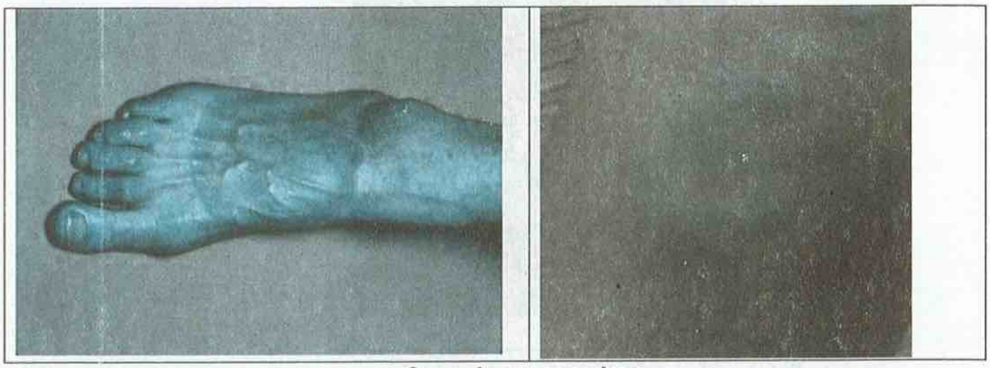
Treatment

- **Localized**: Observation. Often self-resolving; topical or intralesional corticosteroids.
- **Generalized**: Systemic therapies like **hydroxychloroquine** or **dapsone**, or phototherapy.

Prognosis

- Localized type resolves in ~2 years. Generalized forms may persist but are benign.

Key Point: Associated with **diabetes mellitus**; treat generalized cases systemically if needed.



Granuloma annulare

Herpes simplex virus (HSV) and skin disorders

Gingivostomatitis

- **Cause**: Primary HSV-1 infection.
- **Features**: Painful oral ulcers, gingival swelling, fever, lymphadenopathy.
- **Common in**: Children.
- **Treatment**: Oral acyclovir, analgesia, hydration.

Cold Sores (Herpes Labialis)

- **Cause**: Recurrent HSV-1 infection.
- **Features**: Vesicles on lips/perioral area, may ulcerate.
- **Triggers**: Stress, sunlight, illness.
- **Treatment**: Topical acyclovir; oral antivirals for severe cases.

Genital Herpes

- **Cause**: HSV-2 (commonly) or HSV-1.
- **Features**: Painful vesicles/ulcers on genitalia, dysuria, systemic symptoms in primary infection.
- **Transmission**: Sexual contact.
- **Treatment**: Oral acyclovir, valacyclovir, or famciclovir. Chronic suppressive therapy for recurrent cases.

Gingivostomatitis , or genital herpes → oral aciclovir
cold sores → topical aciclovir

Genital Herpes & Pregnancy

- **elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation**

Molluscum contagiosum

Definition: A common skin infection caused by molluscum contagiosum virus (MCV), DNA poxvirus

Transmission: Direct skin contact (contact sports, sexually transmitted), autoinoculation or indirectly via fomites (contaminated surfaces) such as shared towels and flannels.

Risk factors:

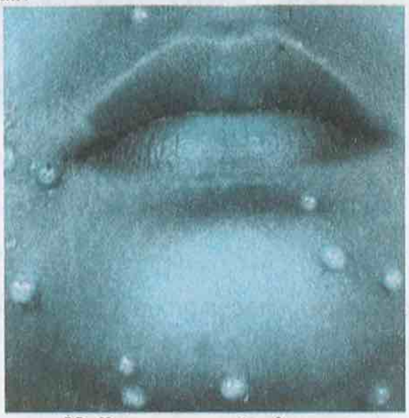
- Most common in children (often in children with atopic eczema)
- Immunosuppression → **HIV testing** if lesions in adults and/or widespread

Presentation

- dome-shaped, smooth, pinkish or pearly white papules with a central umbilication, which are up to 5 mm in diameter. commonly seen on the trunk and in flexures.

Treatment

- Usually self-limiting condition → **Watchful waiting** (especially in children)
- Self-care advice: avoid direct contact and sharing towels . Exclusion from school, gym, or swimming is not necessary.
- For cosmetic or lesions in the genital area:
  - ⇨ Cryotherapy is the first-line treatment
  - ⇨ Topical cantharidin



Molluscum contagiosum

Impetigo

Impetigo is a superficial bacterial skin infection usually caused by either *Staphylcoccus aureus* or *Streptococcus pyogenes.*

Features

- 'golden', crusted skin lesions typically found around the mouth
- very contagious

Management

- **Limited, localised disease**
  - ⇨ **topical fusidic acid is first-line**
  - ⇨ topical retapamulin is used second-line if fusidic acid has been ineffective or is not tolerated
  - ⇨ MRSA is not susceptible to either fusidic acid or retapamulin. Topical mupirocin (Bactroban) should therefore be used in this situation
- **Extensive disease**
  - ⇨ oral flucloxacillin
  - ⇨ oral erythromycin if penicillin allergic

Impetigo - topical fusidic acid → oral flucloxacillin / topical retapamulin

Erysipelas

Definition

- Erysipelas is a *Streptococcus pyogenes* (a group A streptococcal bacterium) infection of the deep dermis and subcutis.

Feature

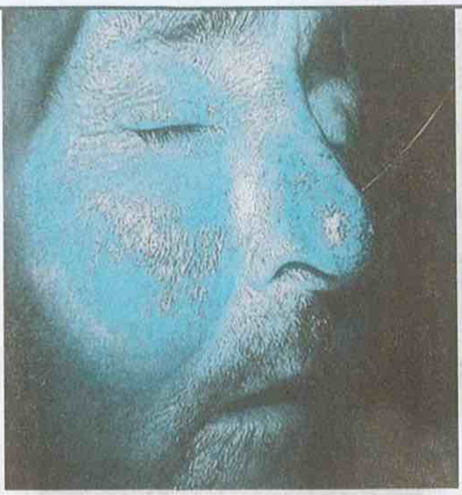
- It is a tender, intensely erythematous, indurated plaque with a sharply demarcated border.
- Its well-defined margin can help differentiate it from other skin infections (eg, cellulitis).

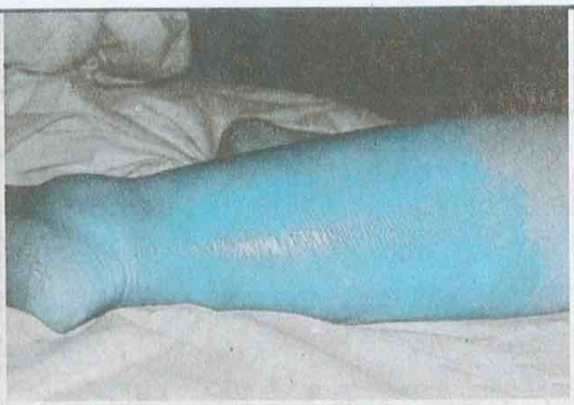
Treatment

- IV antibiotics such as benzylpenicillin and erythromycin.
- **In a penicillin allergic patient a macrolide is the drug of choice** .There is a 10% cross allergy between cephalosporins and penicillins.

Complications

- sepsis
- cerebral abscess
- venous sinus thrombosis.


Well-demarcated, erythematous plaque of erysipelas.



Lichen planus

Definition

- Lichen planus is a skin disorder of unknown aetiology, most probably being immune mediated.

Features

- itchy, papular rash most common on the palms, soles, genitalia and flexor surfaces of arms
- rash often polygonal in shape, 'white-lace' pattern on the surface (Wickham's striae)
- Koebner phenomenon may be seen (new skin lesions appearing at the site of trauma)
- oral involvement in around 50% of patients
- nails: thinning of nail plate, longitudinal ridging
- **Fibrin deposits at the basement membrane zone** are found in cases of lichen planus , although immunofluorescence studies are uncommonly done to diagnose it.

Lichen planus

Lichenoid drug eruptions - causes:

- gold
- quinine
- thiazides

Management

- topical steroids are the mainstay of treatment
- extensive lichen planus may require oral steroids or immunosuppression

Koebner phenomenon:

Describes skin lesions which appear at the site of injury. It is seen in:

- psoriasis
- vitiligo
- warts
- lichen planus
- lichen sclerosus
- molluscum contagiosum

Lichen

- planus: purple, pruritic, papular, polygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common
- sclerosus: itchy white spots typically seen on the vulva of elderly women

Lichen sclerosus

Definition

- Lichen sclerosus was previously termed lichen sclerosus et atrophicus.
- It is an inflammatory condition which usually **affects the genitalia and is more common in elderly females.**
- Lichen sclerosus leads to atrophy of the epidermis with white plaques forming

Features

- itch is prominent

Diagnosis

- usually made on clinical grounds but a biopsy may be performed if atypical features are present*

Management

- topical steroids and emollients

Follow-up

- increased risk of vulval cancer

Skin Biopsy Guidance

- **Not routinely needed** if diagnosis can be made clinically.
- **Indications for biopsy**:
  - Atypical features or diagnostic uncertainty.
  - Lack of response to treatment.
  - Suspicion of vulval intraepithelial neoplasia (VIN) or cancer.
- **Indications for biopsy during follow-up**:
  1. Persistent hyperkeratosis, erosion, erythema, or new warty/papular lesions (neoplastic suspicion).
  2. Non-response to adequate treatment.
  3. Extragenital lichen sclerosus (LS) with morphoea-like features.
  4. Pigmented areas (rule out melanocytic abnormalities).
  5. When second-line therapy is planned.

Lichen simplex chronicus (LSC)

Definition:

- Localized thickening of skin due to chronic scratching or rubbing.

Features:

- Hyperpigmented, scaly, lichenified plaques.

Common Sites:

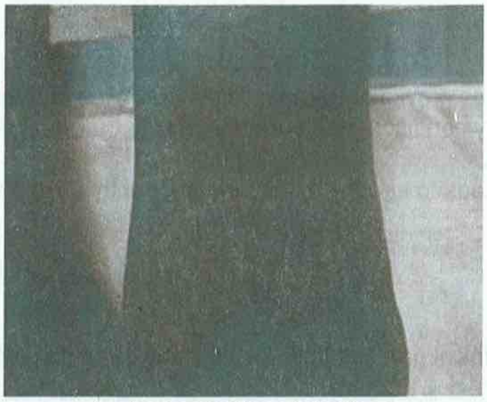
- Ankles, neck, wrists, scalp.

Triggers:

- Stress, pruritic conditions (eczema, psoriasis).

Treatment:

- Topical steroids (reduce inflammation).
- Antihistamines (control itching).
- Behavioural therapy (address scratching habit).



Lichen simplex chronicus

Lichen amyloidosis

Definition: Localized deposition of amyloid in the skin, leading to itchy, hyperpigmented, scaly papules.

Features:

- Pruritic, firm, brown or skin-coloured papules.
- Often coalesce into plaques.
- Commonly affects **shins** and **extensor surfaces.**

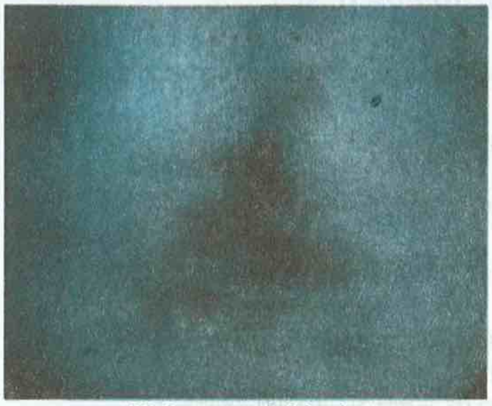
Causes: Chronic friction, genetic predisposition, or underlying systemic amyloidosis.

Diagnosis:

- Clinical appearance.
- Skin biopsy: Confirms amyloid deposits in the dermis (stained with Congo red).

Treatment:

- Emollients and antihistamines for symptom relief.
- Topical steroids or calcineurin inhibitors to reduce inflammation.
- Laser therapy or dermabrasion for refractory cases.



Lichen amyloidosis

Pityriasis rosea

Definition

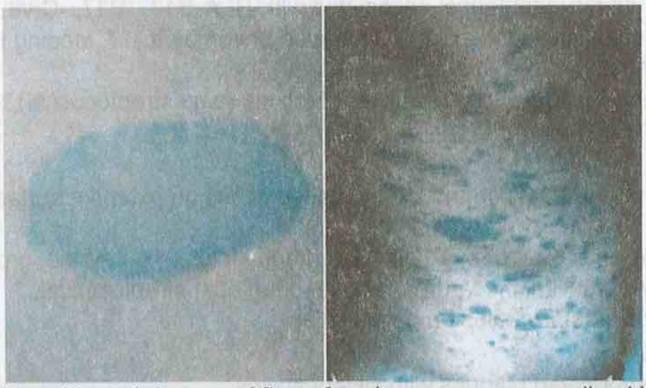
- describes an acute, self-limiting rash which tends to affect young adults. occurs most commonly in people between the ages of 10 and 35 years.
- The aetiology is not fully understood but is thought that herpes hominis virus 7 (HHV-7) may play a role. does not appear to be contagious;
- aetiology is unknown

Features

- herald patch (usually on trunk)
- followed by **erythematous, oval, scaly patches** which follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
- can be pruritic or asymptomatic

Management

- self-limiting, usually disappears after 4-12 weeks
- moisturisers can help the pruritus



On the left a typical herald patch is seen. After a few days a more generalised 'fir-tree' rash appears

Pityriasis versicolor

Definition

- also called tinea versicolor, is a superficial cutaneous fungal infection caused by Malassezia furfur (formerly termed Pityrosporum ovale)

Features

- most commonly affects trunk
- patches may be hypopigmented, pink or brown (hence versicolor)
- scale is common
- mild pruritus

Predisposing factors

- occurs in healthy individuals
- immunosuppression
- malnutrition
- Cushing's

Management

- topical antifungal. NICE Clinical Knowledge Summaries advise ketoconazole shampoo as this is more cost effective for large areas
- **Topical selenium sulphide**
- if extensive disease or failure to respond to topical treatment then consider oral itraconazole 200 mg once a day for seven days.

Psoriasis

Definition

- A chronic, relapsing inflammatory skin condition characterized by erythematous, well-demarcated plaques covered with silvery scales.

Epidemiology

- **Prevalence:** ~2%.
- **Peak Incidence:** 16–22 years and 57–60 years.
- **Gender:** Equal distribution between males and females.

Pathophysiology

- **Genetic:** Polygenic inheritance; associated with **HLA-B13, -B17, -Cw6**.
- **Immunological:** T-cell mediated inflammation driven by **IL-17**, leading to keratinocyte hyperproliferation.
- **Environmental Triggers:** Skin trauma, infections (e.g., streptococcal), stress, and sunlight (improves symptoms).

Subtypes

1. **Plaque Psoriasis:** Most common; red, scaly patches on extensor surfaces, sacrum, and scalp.
2. **Flexural Psoriasis:** Smooth, red plaques in body folds (e.g., axillae, groin).
3. **Guttate Psoriasis:** Small, teardrop lesions; often post-streptococcal.
4. **Pustular Psoriasis:** Pustules on palms/soles.

Clinical Features

- **Skin:** Well-demarcated plaques with silvery scales.
- **Nails:** Pitting, onycholysis.
- **Koebner Phenomenon:** Lesions at trauma sites.
- **Auspitz Sign:** Pinpoint bleeding when scales removed.
- **Scalp Psoriasis:** Common, causes telogen effluvium.

Complications

- **Psoriatic Arthritis:** Affects ~10%.
- **Metabolic Syndrome:** Increased risk.
- **Cardiovascular Disease:** Elevated risk.
- **Psychological:** Anxiety and depression.

Diagnosis

- **Clinical:** Based on characteristic lesions.
- **Skin Biopsy:** Rarely needed; shows hyperkeratosis, parakeratosis, and Munro's microabscesses.

Exacerbating Factors

- Trauma, alcohol, infections.
- Drugs: **Beta blockers, lithium, NSAIDs, antimalarials, ACE inhibitors.**
- **Systemic Steroid Withdrawal:** Causes severe rebound flares.

Management

General Principles

- Regular emollients to reduce scaling and itching.
- Avoid triggers (e.g., trauma, specific drugs).

Chronic Plaque Psoriasis

1. **First-Line:** Potent corticosteroid once daily + vitamin D analogue once daily for up to 4 weeks.
2. **Second-Line:** Vitamin D analogue twice daily if no improvement after 8 weeks.
3. **Third-Line:** Potent corticosteroid twice daily or coal tar preparations.

Scalp Psoriasis

1. Potent corticosteroids (e.g., shampoos, mousses) for 4 weeks.
2. Scale removal agents (salicylic acid, oils) if no improvement.

Face/Flexural/Genital Psoriasis

- Mild corticosteroids for 2 weeks (e.g., clobetasone butyrate).

Secondary Care Management

- **Phototherapy**
  - **Narrowband UVB:** First-line phototherapy.
  - **PUVA:** For refractory cases (psoralen + UVA).
- **Systemic Therapy**
  - **Methotrexate:** First-line for extensive psoriasis or joint involvement.
  - **Ciclosporin:** For rapid control or short-term use.
  - **Acitretin:** For pustular psoriasis or when others fail.
  - **Biologics:**
    - **Anti-TNF agents:** Etanercept, infliximab.
    - **Anti-IL-17 agents:** Brodalumab, ixekizumab.
    - **Ustekinumab (IL-12/IL-23 blocker):** For severe cases; TB and hepatitis screening required pre-treatment.

Special Considerations

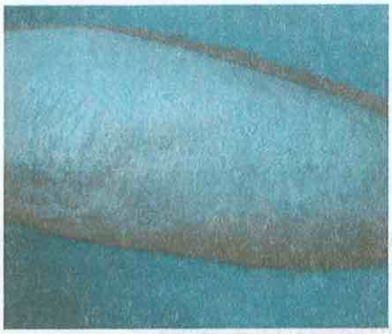
- **Oral Steroids:** Contraindicated due to rebound flares.
- **Pregnancy:** Avoid vitamin D analogues and certain systemic drugs (e.g., methotrexate, acitretin).

Guttate Psoriasis

- **Presentation:** Teardrop-shaped papules, often post-streptococcal infection.
- **Management:**
  1. **Mild (<10% BSA):** Topical treatment or observation (self-resolves in 2–3 months).
  2. **Widespread (>10% BSA):** Urgent dermatology referral for UVB phototherapy.

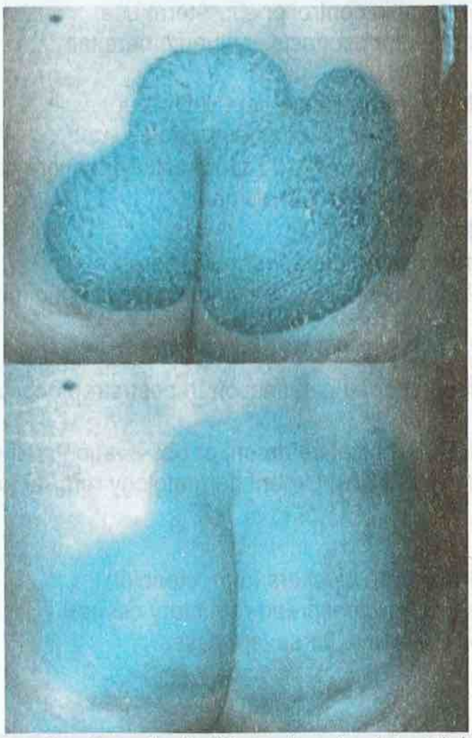
Key Notes for MRCP

1. **Most Concerning Drug:** Beta blockers (e.g., atenolol).
2. **PUVA:** Safe and effective in widespread refractory cases.
3. **Ixekizumab:** Anti-IL-17 effective for severe cases.



Psoriasis: common triggers are beta-blockers and lithium

Topical potent corticosteroid + vitamin D analogue is first-line for chronic plaque psoriasis



A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

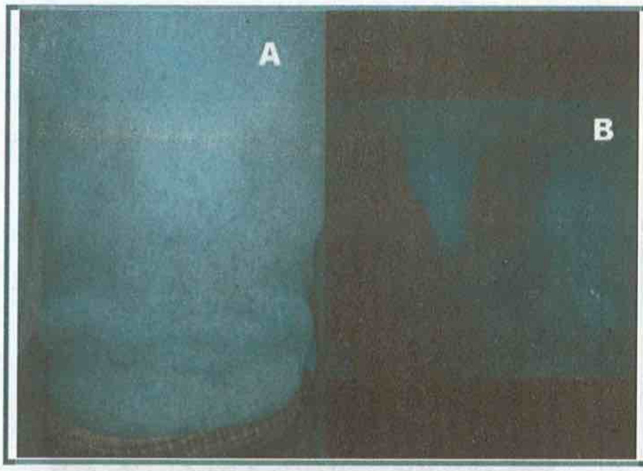
Scalp psoriasis - first-line treatment is topical potent corticosteroids

Flexural psoriasis - topical steroid

Guttate psoriasis

Differentiating guttate psoriasis and pityriasis rosea

	Guttate psoriasis	Pityriasis rosea
Prodrome	Classically preceded by a streptococcal sore throat 2-4 weeks	Many patients report recent respiratory tract infections but this is not common in questions
Appearance	'Tear drop', scaly papules on the trunk and limbs	Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions. May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
Treatment / natural history	Most cases resolve spontaneously within 2-3 months Topical agents as per psoriasis UVB phototherapy	Self-limiting, resolves after around 6 weeks



Guttate psoriasis

- A 46-year-old man presents with an extensive pruritic rash shown in picture A.
- Two weeks previously he had a sore throat with the appearance shown in picture B.

Pyoderma gangrenosum

Overview

- Pyoderma gangrenosum typically is an expanding ulcer with a polycyclic or serpiginous outline and a characteristic undermined bluish edge.
- The pathogenesis is unknown, and is presumed to be immunological.

Features

- typically on the lower limbs
  - ⇨ It is most common on the lower limb and in scars or sites of previous trauma.
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

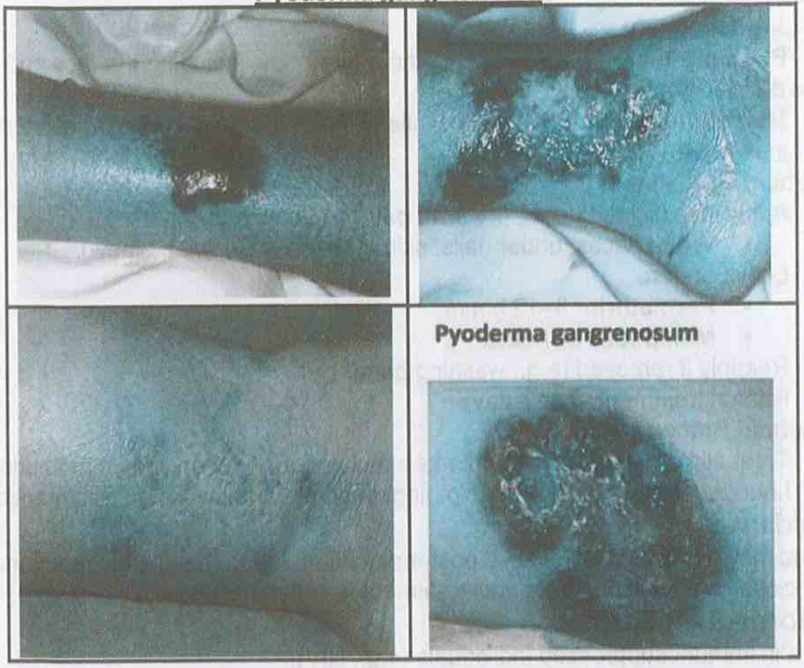
Causes

- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's
  - ⇨ Estimates of the prevalence in inflammatory bowel disease (IBD) range between 2% and 5%.
  - ⇨ It tends to be associated with colonic involvement and is perhaps slightly more common in patients with UC.
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

Pyoderma gangrenosum



Scabies

Definition

- A parasitic infestation caused by the mite *Sarcoptes scabiei*.
- Transmitted by prolonged skin-to-skin contact.

Pathophysiology

- Mites burrow into the stratum corneum, laying eggs.
- **Pruritus:** Caused by a delayed type IV hypersensitivity reaction to mites/eggs, occurring ~30 days after initial infection.

Clinical Features

- **Primary Symptoms:**
  - **Widespread pruritus:** Especially at night.
  - **Burrows:** Pathognomonic linear lesions, commonly found:
    - Sides of fingers.
    - Interdigital webs.
    - Flexor aspects of wrists.
    - Web-spaces and around the nipples.
  - In infants, the face and scalp may also be affected.
- **Secondary Features:**
  - Excoriations and secondary infections due to scratching.

Management

- **First-Line Treatment:**
  - **Permethrin 5% cream**: Apply to the entire body, including the face and scalp.
- **Second-Line Treatment:**
  - **Malathion 0.5% lotion**: Apply similarly if permethrin is contraindicated or ineffective.
- **Treatment Guidelines:**
  - Apply insecticide to cool, dry skin, paying attention to:
    - Web-spaces, under nails, skin creases (e.g., wrist, elbow).
  - Leave on for:
    - **Permethrin:** 8–12 hours.
    - **Malathion:** 24 hours.
  - Reapply if removed (e.g., washing hands).
  - Repeat treatment after **7 days.**
- **Household Precautions:**
  - Treat all household/close contacts simultaneously, even if asymptomatic.
  - Launder, iron, or tumble-dry clothing, bedding, and towels on treatment day.

Patient Guidance

- Pruritus may persist for 4–6 weeks post-eradication due to the allergic reaction.
- Avoid close contact with others until treatment is complete.

Crusted (Norwegian) Scabies

- Occurs in immunosuppressed individuals (e.g., HIV).
- Features:
  - Crusted, thickened skin teeming with mites.
  - Highly contagious.
- **Treatment:**
  - **Ivermectin** (oral).
  - Strict isolation to prevent transmission.

Scabies

Seborrhoeic dermatitis

Definition

- Chronic dermatitis caused by an inflammatory reaction linked to the proliferation of *Malassezia furfur* (formerly *Pityrosporum ovale*), a normal skin fungus.

Epidemiology

- Affects ~2% of the general population.
- More prevalent in individuals with **HIV** (up to 80%) and **Parkinson's disease.**

Clinical Features

- **Skin Lesions:**
  - Eczematous plaques in **sebum-rich areas**:
    - Scalp (dandruff).
    - Periorbital, auricular, and nasolabial folds.
  - Can lead to **otitis externa** and **blepharitis**.
- **Scalp Disease:**
  - Dandruff: Scaly patches in hair-bearing areas; uninflamed form.

Associated Conditions

- **HIV:** High prevalence; consider **HIV testing** in severe or atypical cases.
- **Parkinson's Disease:** Increased prevalence.

Management

Scalp Disease

- **First-Line:**
  - Over-the-counter shampoos:
    - **Zinc pyrithione** (e.g., Head & Shoulders).
    - **Coal tar** (e.g., Neutrogena T/Gel).
- **Second-Line:**
  - **Ketoconazole shampoo.**
- **Additional Options:**
  - **Selenium sulphide.**
  - **Topical corticosteroids** (short-term use).

Face and Body Disease

- **Topical Antifungals:**
  - **Ketoconazole cream** (first-line).
- **Topical Corticosteroids:**
  - Useful for short-term control during flares.

Key Points

- Seborrhoeic dermatitis is recurrent and challenging to treat.
- HIV and Parkinson's patients are at higher risk; severe cases may warrant **HIV testing**.
- Combination therapies (antifungals and corticosteroids) are often needed for effective control.

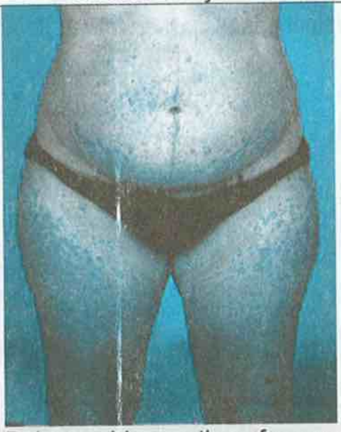
Seborrhoeic dermatitis
- ⇨ **the most useful next step → HIV testing**
- ⇨ **in patients with HIV the prevalence of seborrheic dermatitis may be as high as 80%.**

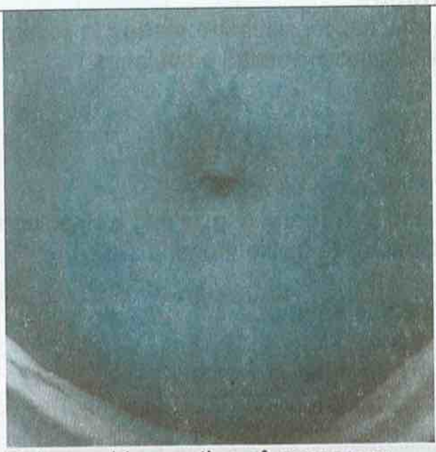
Seborrhoeic dermatitis - first-line treatment is topical ketoconazole

Skin disorder in pregnancy

Polymorphic eruption of pregnancy

- also known as Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP)
- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used


Polymorphic eruption of pregnancy

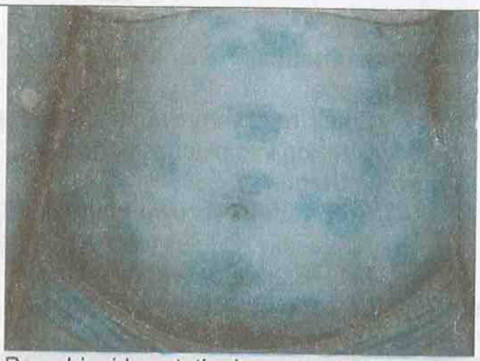

Polymorphic eruption of pregnancy

> Polymorphic eruption of pregnancy is not associated with blistering

Pemphigoid gestationis

- **Definition**
  - ⇨ bullous disorder that typically develops in the second or third trimester, beginning with urticarial lesions and blisters on the anterior abdominal wall surrounding the umbilicus.
- **Features**
  - ⇨ pruritic blistering lesions
  - ⇨ often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
  - ⇨ usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- **Diagnosis**
  - ⇨ A perilesional skin biopsy demonstrating linear C3 deposition at the dermoepidermal junction would confirm the diagnosis.
- **Treatment**
  - ⇨ oral corticosteroids are usually required

Pemphigoid gestationis


Pemphigoid gestationis

Melasma

- Melasma is a benign but relatively common skin condition which can appear in pregnancy.
- it may resolve a few months after delivery.

Chloasma

- **Overview**
  - ⇨ Chloasma is a hormonally stimulated increase in melanogenesis that mainly appears on the face.
  - ⇨ The pigment is augmented by sunlight
  - ⇨ On testing, levels of melanocyte-stimulating hormone are normal
  - ⇨ more likely to occur in women with darker skin tones
- **Causes**
  - ⇨ **Pregnancy**
  - ⇨ combined oral contraceptive pill
- **Treatment**
  - ⇨ The pigmentation may take many months to resolve after parturition or pill discontinuation
  - ⇨ avoid prolonged sunlight exposure or to use a sunblock

Lupus Vulgaris

Definition

- Lupus vulgaris is the most common form of **cutaneous tuberculosis**. It is a **chronic, progressive granulomatous skin infection** caused by *Mycobacterium tuberculosis* in individuals with moderate immunity.

Pathophysiology

- Results from:
  - **Endogenous reactivation** of latent TB.
  - **Hematogenous, lymphatic, or contiguous spread** of TB from another focus (e.g., lymph nodes, bones).
- Immune response leads to granuloma formation with **caseating necrosis**.

Clinical Features

- **Lesion Characteristics**:
  - **Initial Stage**:
    - Small, reddish-brown macules or papules.
    - Develop into plaques or nodules.
  - **Chronic Stage**:
    - **Soft, reddish-brown plaques** with irregular borders.
    - Apple-jelly nodules visible on **diascopy** (pressing with a glass slide).
    - May ulcerate or scar over time.
- **Common Sites**:
  - Face (cheeks, nose).
  - Extremities.
- **Progression**:
  - Slow and indolent course.
  - May lead to **scarring** and **deformity** if untreated.

Diagnosis

- **Clinical Examination**:
  - Classic appearance of plaques with apple-jelly nodules on diascopy.
- **Histopathology**:
  - Granulomas with **caseating necrosis**.
  - Langhans giant cells.
- **Microbiological Tests**:
  - **Acid-fast bacilli (AFB) staining**: Often negative due to low bacterial load.
  - **Mycobacterial culture**: Lowenstein-Jensen medium (may take weeks).
  - **PCR**: Rapid detection of *Mycobacterium tuberculosis*.
- **Mantoux Test (Tuberculin Skin Test)**:
  - Positive in most cases, indicating prior TB exposure.
- **Imaging**:
  - To identify systemic TB (e.g., **chest X-ray** for pulmonary TB).

Complications

- **Chronic ulceration**.
- **Scarring** leading to disfigurement.
- Risk of **squamous cell carcinoma** in long-standing lesions.

Treatment

- **First-Line Anti-Tuberculosis Therapy (ATT)**:
  - **Isoniazid (300 mg/day)**: Inhibits mycolic acid synthesis.
  - **Rifampicin (600 mg/day)**: Inhibits RNA polymerase.
  - **Pyrazinamide (20–25 mg/kg/day)**: Disrupts mycobacterial membranes.
  - **Ethambutol (15 mg/kg/day)**: Inhibits cell wall synthesis.
  - Duration: **6–9 months** (2 months intensive phase, 4–7 months continuation).
- **Adjunctive Therapy**:
  - **Topical corticosteroids**: Reduce inflammation in active lesions.
  - **Surgical excision**: For non-healing ulcers or cosmetic reasons.

Key Points for MRCP Candidates

- **Lupus vulgaris** is the most common form of cutaneous TB.
- **Apple-jelly nodules** on diascopy are a classic finding.
- Diagnosis is based on histopathology, culture, or PCR, as AFB staining is often negative.
- **Early ATT** prevents complications like scarring and malignancy.

lupus vulgaris is the most common form of cutaneous TB (accounts for 50% of TB associated skin disorders)

Spider nevi

Definition

- Vascular lesion with a central arteriole and radiating capillaries resembling a spider's web.

Causes

- **Physiological**: Pregnancy, children.
- **Pathological**: Liver disease (e.g., cirrhosis), hyperthyroidism, hormonal therapy.

Features

- **Appearance**: Central red dot with radiating vessels; blanches on pressure.
- **Sites**: Face, neck, chest, arms.

Diagnosis

- Clinical: Blanching lesion.
- Investigate liver disease if multiple (>5): LFTs, ultrasound.

Treatment

- Address underlying cause.
- Cosmetic: Laser or electrocoagulation.

The cause of the spider nevi → patients cannot metabolize circulating estrogen

forehead lesion (spider nevus (nevus araneus))

Tinea

Definition

Tinea refers to **dermatophyte fungal infections** of keratinised tissue. It is classified based on the affected body part:

1. **Tinea capitis**: Scalp.
2. **Tinea corporis**: Trunk, legs, or arms.
3. **Tinea pedis**: Feet.

Tinea Capitis (Scalp Ringworm)

- **Key Features**
  - Affects children and may cause **scarring alopecia**.
  - **Kerion**: A boggy, pustular mass that can form if untreated.
- **Causes**
  - **UK/USA**: *Trichophyton tonsurans* (>90%).
  - **Zoonotic**: *Microsporum canis* (from cats/dogs).

- **Diagnosis**
  - **Scalp scrapings**: Most useful test.
  - **Wood's lamp**:
    - *Microsporum canis*: Fluoresces green.
    - *Trichophyton tonsurans*: No fluorescence.
- **Management (CKS Guidelines)**
  - **Oral antifungals**:
    - **Terbinafine**: 4-week course for ***T. tonsurans***. Preferred despite unlicensed use in children.
    - **Griseofulvin**: 2–4 months for *Microsporum* infections (fungistatic).
  - **Topical treatment**: **Ketoconazole shampoo**: Reduces transmission (first 2 weeks).

Types of Tinea

Feature	Tinea Capitis	Tinea Corporis	Tinea Pedis
Location	Scalp	Trunk, legs, arms	Feet
Affected Population	Primarily children	Any age group	Adults (common in athletes)
Appearance	Patches of hair loss, scaling, or kerion	Annular, scaly plaques with central clearing	Scaling, fissures, erythema, pruritus
Cause	*Trichophyton tonsurans*, *Microsporum canis*	*Trichophyton rubrum*, *T. mentagrophytes*	*Trichophyton rubrum*, *T. interdigitale*
Transmission	Direct contact, fomites, zoonotic	Direct contact, fomites	Contaminated surfaces, humid areas
Diagnosis	Scalp scrapings, Wood's lamp	Skin scrapings, KOH preparation	Skin scrapings, KOH preparation
Management	Oral antifungals, ketoconazole shampoo	Topical antifungals (e.g., clotrimazole), oral antifungals for extensive cases	Topical antifungals (e.g., terbinafine), oral antifungals for chronic cases

Image showing a kerion

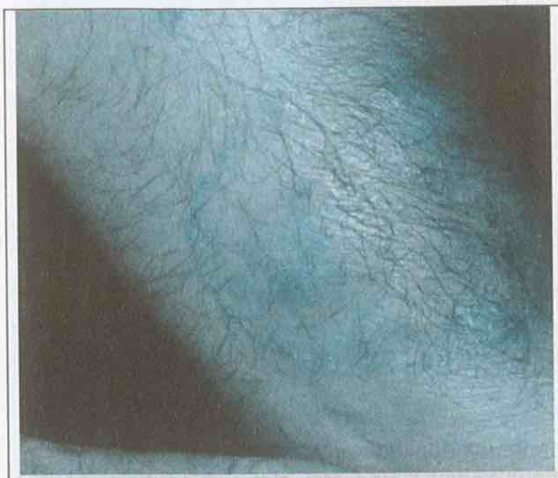


Image showing tinea corporis

Image showing tinea corporis. Note the well defined border

Tinea Incognito

- ⇨ **Tinea incognito is a modified fungal infection caused by inappropriate use of topical corticosteroids, leading to atypical presentations like reduced inflammation, altered lesion borders, and widespread infection, complicating diagnosis and delaying treatment.**

What is the cause for tinea incognito?

- ⇨ **Inappropriate treatment with steroid cream**

Griseofulvin

The enzyme that is most likely induced by griseofulvin requires which of the following cofactors?

- ➲ **Vitamin B_6**
  - Griseofulvin is a microtubule poison that is used to treat skin and nail dermatophytoses
  - strong inducer of cytochrome P450 enzymes.
  - CYP450 enzymes require heme for proper function, and thus inducers of CYP450 increase heme synthesis.

Vitiligo

Definition

- Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin.

Epidemiology

- It is thought to affect around 1% of the population
- symptoms typically develop by the age of 20-30 years.

Features

- well demarcated patches of depigmented skin
- the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

Associated conditions

- type 1 diabetes mellitus
- Addison's disease
- autoimmune thyroid disorders
- pernicious anaemia
- alopecia areata

Diagnosis

- Diagnosis is made clinically
- anti-melanocyte antibodies
- can be confirmed using a skin biopsy.

Management

- sun block for affected areas of skin
- camouflage make-up
- topical corticosteroids may reverse the changes if applied early
- there may also be a role for topical tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients

Vitiligo

Angular stomatitis

Definition

- **Inflammation of the corners of the mouth** (labial commissures) causing pain, cracking, and fissures.

Causes

- **Infective:**
  - **Fungal:** *Candida albicans.*
  - **Bacterial:** *Staphylococcus aureus.*
- **Nutritional Deficiencies:**
  - **Iron deficiency.**
  - **Vitamin B2 (riboflavin) deficiency.**
- **Systemic Conditions:**
  - Diabetes mellitus.
  - Immunosuppression.

Clinical Features

- Painful **cracks, redness, and fissures** at the mouth corners.
- May be accompanied by crusting or secondary infection.

Diagnosis

- Clinical examination.
- Swabs or scrapings for **fungal culture** or **bacterial identification**.
- Blood tests for **iron studies** or **vitamin deficiencies** if systemic causes are suspected.

Management

- **Treat Underlying Cause**:
  - Correct **iron** or **vitamin B2 deficiency**.
  - Address ill-fitting dentures or salivary pooling.
- **Topical Therapy**:
  - **Antifungals**: Clotrimazole or miconazole for fungal infections.
  - **Antibacterials**: Fusidic acid or mupirocin for bacterial infections.

Venous ulceration

Definition

- **Venous ulcers** are chronic skin ulcers caused by **venous stasis**, **typically occurring above the medial malleolus**, due to chronic venous insufficiency.

Risk Factors

- **Obesity**.
- **Varicose veins**.
- **History of deep vein thrombosis (DVT)**.

Pathophysiology

- **Venous stasis** → Increased **capillary pressure** → Fibrosis and poor skin nourishment → Ulceration.

Investigations

- **Ankle-Brachial Pressure Index (ABPI)**:
  - Normal: **0.9–1.2**.
  - Arterial disease: **<0.9**.
  - Arterial calcification (false-negative): **>1.3** (e.g., in diabetics).
  - Always perform ABPI before starting compression therapy to exclude arterial disease.

Management

- **Compression Therapy** (**mainstay of treatment**):
  - Four-layer bandaging to improve venous return and reduce venous hypertension.
  - **ABPI >1.0** required before starting compression to exclude significant arterial disease.
- **Medications**:
  - **Pentoxifylline**: A peripheral vasodilator that improves healing.
  - **Flavonoids**: Small evidence base for benefit.
- **Other Therapies** (limited evidence):
  - Hydrocolloid dressings.
  - Topical growth factors.
  - Ultrasound therapy.
  - Intermittent pneumatic compression.

Key Points

- Always assess for arterial disease before compression therapy.
- Compression bandaging is the **only proven effective treatment** for venous ulcers.
- ABPI <0.9 or >1.3 suggests the need for further evaluation of arterial disease.

> Management of venous ulceration - compression bandaging

Pressure ulcers

Overview

- Develop in patients with **reduced mobility** due to illness, paralysis, or advanced age.
- Commonly occur over **bony prominences** (e.g., sacrum, heels).

Risk Factors:

1. **Malnourishment**.
2. **Incontinence**.
3. **Immobility**.
4. **Pain** (reduces movement).

Screening:

- **Waterlow Score**: Assesses risk based on BMI, nutrition, skin type, mobility, and continence.

Grading of Pressure Ulcers (European Pressure Ulcer Advisory Panel)

Grade	Findings
1	Non-blanchable erythema of intact skin. May include warmth, oedema, or hardness.
2	Partial thickness skin loss involving epidermis or dermis. Appears as an abrasion or blister.
3	Full thickness skin loss with damage or necrosis of subcutaneous tissue. May extend to fascia.
4	Extensive tissue destruction, necrosis, or damage to muscle, bone, or supporting structures.

Management

- **Wound Care**:
  - Maintain a **moist wound environment** (e.g., hydrocolloid dressings, hydrogels).
  - Avoid soap to prevent drying.
- **Antibiotics**:
  - Avoid routine wound swabs (ulcers often colonised with bacteria).
  - Use systemic antibiotics only if there is evidence of **cellulitis**.
- **Specialist Referral**:
  - **Tissue Viability Nurse**: For wound assessment and management.
  - **Surgical Debridement**: For selected wounds with necrotic tissue.

> Waterlow score - used to identify patients at risk of pressure sores

Keloid scars

Definition

- Keloid scars are **excessive, abnormal scar formations** that extend beyond the boundaries of the original wound, caused by an overactive wound healing process.

Pathophysiology

- Excessive deposition of **collagen**, particularly type I and III, during wound healing.
- Associated with **fibroblast hyperproliferation** and dysregulation of growth factors (e.g., TGF-β).

Risk Factors

- **Genetic predisposition**:
  - **More common in people with dark skin**
- **Site-specific**:
  - Common on the chest, shoulders, upper back, earlobes, and cheeks.
- **More commonly in young adults, rare in the elderly**

Clinical Features

- Firm, raised, and shiny scar tissue.
- May cause **pain, pruritus**, or discomfort.
- Extends beyond the original wound margin, unlike hypertrophic scars.

Management

- **First-line Therapy**:
  - **Intralesional corticosteroids** (e.g., triamcinolone): Reduces inflammation and fibroblast activity.
- **Other Interventions**:
  - **Cryotherapy**: Freezes and reduces scar tissue (effective for small keloids).
  - **Laser therapy**: Reduces scar volume and erythema.
  - **Surgical excision**: High recurrence risk unless combined with corticosteroids or radiation.
- **Emerging Treatments**:
  - **5-fluorouracil (5-FU)** injections.
  - **Imiquimod cream** after surgery.

> Keloid scars are most common on the sternum

> Keloid scars - more common in young, black, male adults

Increased skin fragility

Definition

- A condition where the skin is prone to tearing or blistering with minimal trauma. It is often a clinical feature in **bullous disorders** and other systemic or dermatological conditions.

Causes

- **Bullous Disorders (Positive Nikolsky's Sign):**
  - **Pemphigus vulgaris**: Autoimmune disease with intraepidermal blistering.
  - **Porphyria cutanea tarda**: Photosensitivity and blistering on sun-exposed areas.
  - **Drug reactions**: Pseudoporphyria caused by drugs like NSAIDs or antibiotics.

- **Non-Bullous Causes:**
  - **Long-term corticosteroid therapy**: Thinning of the dermis and impaired collagen synthesis.
  - **Ehlers-Danlos syndrome**: Genetic connective tissue disorder with hyperextensible skin and fragility.
  - **Scurvy (vitamin C deficiency)**: Impaired collagen synthesis due to lack of ascorbic acid.

Clinical testing

- Nikolsky's sign: Gentle rubbing of the skin causes epidermal detachment in bullous disorders like pemphigus vulgaris.

Key Points

- Skin fragility in bullous disorders is tested with **Nikolsky's sign**.
- Non-bullous causes often involve **connective tissue defects** or **collagen abnormalities**.

Livedo reticularis (LR)

Definition

- A vascular condition characterized by a **lace-like, purple discoloration** of the skin due to impaired blood flow in cutaneous vessels.

Types

1. **Physiological LR**: most common
   - Benign, transient, and resolves with warmth.
   - Common in cold environments.
2. **Pathological LR**:
   - Persistent or recurrent, often associated with systemic or vascular diseases.

Causes

1. **Physiological**: Cold exposure.
2. **Pathological**:
   - **Autoimmune diseases**: Lupus, antiphospholipid syndrome.
   - **Vascular disorders**: Vasculitis, cholesterol embolism.
   - **Infectious diseases**: Syphilis, TB.
   - **Hematological conditions**: Polycythemia vera, cryoglobulinemia.
   - **Medications**: Amantadine, Minocycline, catecholamines.

Features

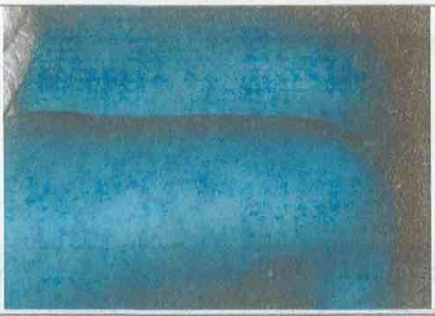
- Reticular (net-like) pattern, red-to-purple discoloration.
- Affects extremities (e.g., legs) more commonly.
- Can be **reversible** (physiological) or **persistent** (pathological).
- **Associated Symptoms (Pathological LR)**
  - Pain, ulceration, or necrosis in severe cases.
  - Systemic symptoms related to underlying conditions (e.g., fever, weight loss, joint pain).

Investigations:

- Blood tests: ANA, antiphospholipid antibodies, cryoglobulins.
- Imaging: Doppler or angiography to assess blood flow.
- Skin biopsy: In suspected vasculitis or embolic conditions.

Management

- **Physiological LR**: Reassurance and avoid cold exposure.
- **Pathological LR**:
  - Treat the **underlying cause** (e.g., anticoagulation for antiphospholipid syndrome, immunosuppression for vasculitis).
  - Supportive care: Warmth, pain management.



Livedo reticularis that does not regress after application of warmth is indicative of an underlying vascular disease and requires treatment.

Hyperhidrosis

Definition:

- Excessive sweating beyond physiological needs, affecting quality of life.

Types

- **Primary**: Localized (e.g., palms, soles, axillae), begins in childhood/adolescence, no sweating during sleep.
- **Secondary**: Generalized, caused by conditions (e.g., hyperthyroidism, diabetes) or medications.

Diagnosis

- Clinical evaluation; rule out secondary causes.

Management

- **Lifestyle**: Aluminium chloride antiperspirants, avoid triggers.
- **Medical**: Anticholinergics (oxybutynin), Botox for localized sweating.
- **Procedures**: Iontophoresis, sympathectomy (severe cases).

Basal cell carcinoma (BCC)

Overview

- Most common **malignant skin tumour**, associated with **excessive sun exposure**.
- Affects **elderly patients** with sun-damaged skin, commonly on the **upper lip**.
- Known as **rodent ulcers**.
- **Slow-growing** and locally invasive; **metastases are rare**.

Genetics

- Linked to mutations in the **Hedgehog signaling pathway**.
- **PTCH1 gene mutations** occur in up to 70% of sporadic cases due to UV exposure.

Clinical Features

- Commonly affects **sun-exposed areas** (e.g., head, neck).
- **Nodular BCC**:
  - **Appearance**: Pearly, flesh-coloured papule with **telangiectasia**.
  - **Progression**: May ulcerate, forming a central crater.
- **Histology**: Palisading nuclei (rows of elongated nuclei).

Management

- **Surgical Removal**:
  - **Mohs surgery**: Minimises excised margins, preserves tissue.
- **Other Treatments**:
  - Curettage, cryotherapy.
  - Topical: **Imiquimod, 5-fluorouracil.**
  - Radiotherapy for inoperable cases.

BCC vs SCC

Feature	Basal Cell Carcinoma (BCC)	Squamous Cell Carcinoma (SCC)
Prevalence	Most common skin cancer	Second most common skin cancer
Location	Upper face (e.g., upper lip)	Lower face (e.g., lower lip, ear, nose)
Metastasis	Rare, kills by local invasion (rodent ulcer)	Can metastasize
Appearance	Pearly papule with telangiectasias and crater	Hyperkeratotic, scaly lesion with crusting/ulcer
Growth	Slow-growing	Rapid and aggressive
Histology	Palisading nuclei	Keratinisation and atypical squamous cells

Key Points

- BCC is **locally invasive** but rarely metastasizes.
- Sun-exposure prevention is crucial for reducing risk.
- **Mohs surgery** is preferred for high-risk areas to minimise recurrence.

Squamous cell carcinoma (SCC)

Overview

- **Second most common non-melanoma skin cancer** worldwide (after BCC).
- Most common **oral cancer**; affects skin, lips, oral cavity, genitals, and lower legs (women).
- More common in **elderly males**.

Precursor Lesions and Variants

- **Actinic Keratosis**:
  - Hyperkeratotic grey-white plaques; precursor to SCC.
- **Bowen's Disease**:
  - In situ SCC.
- **Keratoacanthoma**:
  - Rapidly growing, cup-shaped SCC variant that may spontaneously resolve.

Risk Factors

- **UV Radiation (UVB)**:
  - Causes **p53 gene mutations**; affects photo-exposed areas (e.g., face, lower lip).
- **Skin Type and Colour**:
  - Higher incidence in light-skinned individuals.
  - Advanced stage at presentation in people of colour.
- **Chronic Conditions**:
  - Chronic scars, burns (*Marjolin ulcer*), draining sinuses.
  - **Immunosuppression** (e.g., post-transplant patients).
- **Infections**:
  - **HPV** and chronic infections.
- **Other Factors**:
  - Smoking, arsenic exposure, ionizing radiation, inherited conditions (e.g., xeroderma pigmentosum).

Clinical Features

- Scaly, crusty lesion with a **red, inflamed base.**
- Common on **lower lip**, often with an ulcerated or hyperkeratotic appearance.

Diagnosis

- **Excisional Biopsy**:
  - Shows **keratin pearls** in well-differentiated tumours.
  - Poorly differentiated tumours lack keratin pearls, have more atypical cells.

Treatment

- **Surgical Excision**:
  - <20 mm diameter: **4 mm margins.**
    - 20 mm diameter: **6 mm margins.**
  - **Mohs Surgery**: Preserves healthy tissue, best for high-risk areas.
- **Non-Surgical Options**:
  - **Cryotherapy** and **topical chemotherapy** (e.g., 5-fluorouracil).
  - **Radiotherapy** for poor surgical candidates.
- **Adjuvant Chemotherapy**:
  - High-risk or advanced cases.

Prevention

- **Sunscreen** to reduce UV exposure and SCC risk.

Prognosis

Good Prognosis	Poor Prognosis
Well-differentiated tumour	Poorly differentiated tumour
<20 mm in diameter	>20 mm in diameter
<2 mm depth	>4 mm depth
No associated diseases	Immunosuppression

Keratoacanthoma (KA)

Overview

- A **low-grade malignancy** originating in the pilosebaceous glands, resembling **squamous cell carcinoma (SCC).**
- May be considered a variant of invasive SCC but is generally **benign**.
- Believed to develop from **hair follicles**, more common in **males** and **middle-aged adults**.
- Characterized by **rapid growth** over weeks to months, often followed by **spontaneous resolution** in 4–6 months.

Features

- Begins as a **smooth dome-shaped papule.**
- Rapidly develops into a **dome-shaped nodule** with a **central crater** filled with **keratin**, resembling a **volcano or crater**.

Treatment

- **Urgent referral to dermatology** for assessment.
- Excision is recommended to:
  - Differentiate from **SCC**.
  - Prevent scarring.
- **Spontaneous regression** is possible within 3 months but may leave a scar.

Key Points

- Resembles SCC; **histopathological confirmation** is often required.
- Lesions are rapidly growing but self-limiting in most cases.

Keratoacanthoma

Malignant melanoma

Overview

- **Origin**: Arises from **melanocytes** in the basal epidermis.
- **Epidemiology**: Third most common skin cancer but **leading cause of skin cancer-related deaths**.
- **Metastasis**: ~20% of patients develop metastatic disease.

Risk Factors

1. **Environmental**:
    - Excessive **UV radiation** (sun exposure, tanning beds).
    - History of **blistering sunburns**.
2. **Genetic**: Family history, **CDKN2A mutation**, **BRAF mutation**.
3. **Skin Type**: Fair skin, freckles, inability to tan.
4. **Pre-existing Lesions**: **Dysplastic nevi**, **congenital nevi**, actinic keratosis.
5. **Medical History**: Previous melanoma, immunosuppression, xeroderma pigmentosum.

ABCDE Mnemonic for Melanoma Features:

- **A**: Asymmetry.
- **B**: Border irregularity.
- **C**: Colour variation.
- **D**: Diameter >7 mm or increasing size.
- **E**: Evolution (changes in size, shape, or nodules).

Prognostic Factors

- **Breslow Depth (tumour thickness): Most important predictor of prognosis.**

Breslow Thickness	5-Year Survival
< 1 mm	95–100%
1–2 mm	80–96%
2.1–4 mm	60–75%
> 4 mm	~50%

Types of Melanoma

- **Superficial Spreading Melanoma**:
    - Most common type.
    - Irregular brown, black, or blue-black lesion with inflammation.

- **Nodular Melanoma**:
  - Rapidly growing, aggressive.
  - May have little melanin; higher metastatic risk.
- **Lentigo Maligna**:
  - Slow-growing melanoma in situ on **sun-exposed skin** (e.g., face of elderly patients).
  - May progress to **lentigo maligna melanoma**.
- **Acral Lentiginous Melanoma**:
  - Common in **African-Americans** and **Asians**.
  - Found on **soles, palms, or under nails.**
  - Often in **non-sun-exposed areas.**
- **Periungual Melanoma**:
  - Lesion in the nail bed; **Hutchinson's sign** (brown pigmentation on the nail fold) is a key clue.

Treatment

- **Localised Disease**: Surgical excision based on Breslow depth.
- **Metastatic Melanoma**:
  - **Vemurafenib**: Targets **BRAF oncogene mutation**.
  - Immunotherapies (e.g., checkpoint inhibitors like nivolumab).

Key Points

- Regular monitoring with **ABCDE criteria** can help early detection.
- **Breslow depth** dictates prognosis and management.

> Melanoma: the invasion depth of the tumour is the single most important prognostic factor

Moles (Melanocytic Nevi)

Definition

- **Moles** are benign growths of **melanocytes** (pigment-producing cells) that appear as pigmented spots or raised lesions on the skin.

Risk Factors

- **Genetics**: Family history of moles or melanoma.
- **Sun Exposure**: UV radiation can stimulate mole formation and increase the risk of malignant transformation.
- **Skin Type**: Fair-skinned individuals with light hair and freckles are at higher risk.

Clinical Features

- **Appearance**:
  - Symmetrical shape.
  - Uniform colour (brown, black, or skin-toned).
  - Regular borders.
  - Usually <6 mm in diameter.
- **Change in Moles**:
  - Growth, colour change, bleeding, or asymmetry may suggest malignant transformation (melanoma).

Diagnosis

- **Dermoscopic Examination**:
  - Assesses mole structure, pigmentation, and vascular patterns.
- **ABCDE Criteria** (to evaluate for melanoma):
  - Asymmetry.
  - Border irregularity.
  - Colour variability.
  - Diameter >6 mm.
  - Evolution or change.

Management

- **Benign Moles**:
  - No treatment needed unless for cosmetic reasons.
  - Monitoring for changes.
- **Suspicious Moles**:
  - **Excisional Biopsy**: For histological analysis if melanoma is suspected.

Complications

- Risk of malignant transformation to **melanoma**, especially for:
  - Dysplastic nevi (atypical moles).
  - Large congenital nevi.

Prevention

- **Sun Protection**:
  - Use sunscreen and avoid excessive sun exposure.
- **Regular Skin Checks**:
  - Self-examination and professional skin checks for high-risk individuals.

Key Points

- Most moles are benign, but monitor for changes (ABCDE criteria).
- Protect against UV radiation to prevent the development and transformation of moles.

Uniform pigmentation is not in itself a suspicious feature of a mole, but colour variegation and irregular border are two of many suspicious features.

Angiosarcoma

Definition

- A rare, aggressive malignancy of **vascular endothelial cells**, affecting the skin, soft tissues, or visceral organs.

Common Sites

1. **Cutaneous**: Head and neck (especially scalp) in elderly.
2. **Visceral**: Liver, breast, and heart.

Risk Factors

- **Chronic lymphedema** (e.g., Stewart-Treves syndrome after mastectomy).
- **Radiation exposure**.
- **Environmental toxins** (e.g., arsenic, vinyl chloride).

Clinical Features

- Bruise-like, violaceous plaques or nodules that may ulcerate.
- Rapid growth and tendency to metastasize.

Diagnosis

- **Biopsy**: Malignant endothelial cells with vascular channels.
- Immunohistochemistry: Positive for CD31, CD34, and VEGF.

Management

- **Surgical excision**: Wide margins.
- **Radiotherapy**: Adjuvant or for unresectable cases.
- **Chemotherapy**: For metastatic disease (e.g., paclitaxel).

Prognosis

- **Poor** due to high metastatic potential; early detection is critical.

Pyogenic granuloma

Definition

- A benign, rapidly growing **vascular lesion** of the skin or mucous membranes, often triggered by trauma or irritation.

Features

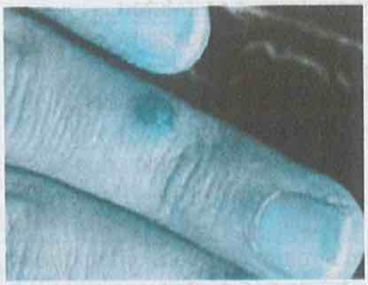
- **Appearance**:
  - Small, red, dome-shaped papule or nodule.
  - **Can bleed easily** and profusely.
- **Location**:
  - Common on the **hands**, **fingers**, **face**, and **oral mucosa**.
- **Triggers**:
  - Trauma, hormonal changes (e.g., pregnancy), or medications (e.g., retinoids).

Diagnosis

- **Clinical**: Based on characteristic appearance and history of rapid growth.
- **Biopsy**: Performed to rule out malignancies such as **amelanotic melanoma** or Kaposi sarcoma.

Management

1. **First-line:**
   - Surgical excision with biopsy.
   - Electrocautery or laser therapy to prevent recurrence.
2. **Alternative:**
   - Cryotherapy for smaller lesions.
   - Topical agents like silver nitrate for mild cases.



Skin disorders associated with malignancy

Paraneoplastic syndromes associated with internal malignancies:

Skin disorder	Associated malignancies
Acanthosis nigricans	Gastric cancer
Acquired ichthyosis	Lymphoma
Acquired hypertrichosis lanuginosa	Gastrointestinal and lung cancer
Dermatomyositis	Ovarian and lung cancer
Erythema gyratum repens	Lung cancer
Erythroderma	Lymphoma
Migratory thrombophlebitis	Pancreatic cancer
Necrolytic migratory erythema	Glucagonoma
Pyoderma gangrenosum (bullous and non-bullous forms)	Myeloproliferative disorders
Sweet's syndrome	Haematological malignancy e.g. Myelodysplasia - tender, purple plaques
Tylosis	Oesophageal cancer

Keratosis

Definition

- **Keratosis** refers to the thickening of the outer layer of the skin (**stratum corneum**) due to excessive keratin production.

Types of Keratosis

Type	Key Features	Common Locations
Seborrheic Keratosis	- Benign, **waxy**, "stuck-on" appearance. - Tan, brown, or black lesions. - Can become pruritic or irritated.	Trunk, face, extremities (spares palms and soles).
Actinic Keratosis (Solar Keratosis)	- Pre-malignant lesion caused by **chronic sun exposure**. - Rough, scaly patch; may progress to squamous cell carcinoma (SCC).	Sun-exposed areas (face, scalp, forearms).
Keratosis Pilaris	- Small, rough, follicular papules due to keratin plugging of hair follicles ("chicken skin").	Extensor surfaces of arms, thighs, buttocks.
Hyperkeratosis	- Thickened stratum corneum, often due to friction or pressure (e.g., calluses or corns).	Palms, soles, pressure areas (feet).

Diagnosis

- **Clinical**:
  - Seborrheic Keratosis: Waxy, "stuck-on" appearance.
  - Actinic Keratosis (Solar Keratosis): Rough, scaly patches on sun-exposed areas.
  - Keratosis Pilaris: Follicular papules ("chicken skin") on extensor surfaces.
  - Hyperkeratosis: Thickened skin on pressure/friction areas.
- **Dermatoscopy**: Not typically required for Keratosis Pilaris
  - Seborrheic Keratosis: : Pseudohorn cysts, milia-like cysts.
  - Actinic Keratosis (Solar Keratosis): Erythematous base with adherent white scale, red dots, and yellowish crusts.
  - Hyperkeratosis: Homogeneous, yellowish thickening.
- **Biopsy**: Rarely needed, only for atypical lesions.

Management

1. **Seborrheic Keratosis**:
   - No treatment required unless symptomatic or cosmetic.
   - Removal: Cryotherapy, shave excision, curettage.
2. **Actinic Keratosis**:
   - **Prevention**: Sun protection, use of sunscreen.
   - Treatment: Cryotherapy, topical 5-fluorouracil, or photodynamic therapy.
3. **Keratosis Pilaris**:
   - Moisturizers with **urea** or **salicylic acid**.
   - Gentle exfoliation and emollients.
4. **Hyperkeratosis**:
   - Padding, proper footwear, and keratolytic agents (e.g., salicylic acid).

Key Points

- **Seborrheic Keratosis**: **Benign epidermal tumor** and **common in older adults**.
- **Actinic Keratosis**: Sun-induced, **pre-malignant**; monitor for progression to SCC.
- **Keratosis Pilaris**: Harmless and often improves with age.

Hyperkeratotic palmar dermatitis

Seborrheic Keratosis

Actinic keratoses affecting the nose
A pink base with a hyperkeratotic top on the nasal bridge - a common site for actinic keratoses

keratosis pilaris

+++++

4th edition 2025

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Psychiatry

Updated

2025

Unexplained Symptoms

Definition

- **Unexplained symptoms** refer to physical complaints that **cannot be fully attributed to a known medical condition** after appropriate evaluation.

Examples

- **Somatisation disorder:**
  - Physical symptoms with no identifiable medical cause, → multiple, recurrent, and varying symptoms (e.g., pain, fatigue).
- **Conversion disorder**
  - typically **involves involuntary loss of motor or sensory function without a physiologic cause , often following an acute stressor.**
- **Dissociative disorder**
  - **involves psychiatric symptoms e.g. Amnesia, fugue, stupor**
- **Malingering** patients consciously fake or exaggerate for secondary gain, such as money, sick leave, or avoidance of responsibilities.

Causes and Contributing Factors

1. **Psychological**: Anxiety, depression, stress, or trauma.
2. **Physiological**: Subtle dysfunctions undetected by standard investigations.
3. **Behavioral**: Health-seeking behaviors or reinforcement of illness identity.

Key Features

- Symptoms often persist despite negative investigations.
- Multiple symptoms across different systems (e.g., fatigue, pain, dizziness).
- Frequently associated with **emotional distress**, health anxiety, or social stressors.

Management

- **Reassurance and Validation**: Acknowledge the patient's distress; avoid dismissing symptoms as "all in the head."
- **Identify triggers**: Explore psychological or social stressors contributing to symptoms.
- **Cognitive Behavioral Therapy (CBT)**
- **Symptom Management** (e.g., pain, sleep disturbances)

Somatisation	**unexplained physical symptoms with (e.g., pain, fatigue). but lacks the neurological features**
Hypochondria	**Excessive worry about having or developing a serious illness (e.g., cancer) despite little or no medical evidence.**
Conversion disorder	**Neurological symptoms (e.g., weakness, paralysis, seizures) with no identifiable medical cause, triggered by stress or trauma.**
Dissociative disorder	**Disruption in memory, identity, or perception (e.g., amnesia, depersonalisation, derealisation, identityconfusion or multiple personality states)**
Malingering	**Deliberate intent to fake symptoms for external gain (e.g., financial compensation, avoiding work).**

Unexplained symptoms
- Somatisation = Symptoms
- hypoChondria = Cancer

Eating disorders

Anorexia Nervosa

- **Definition**
  - An eating disorder characterized by **intense fear of weight gain**, **distorted body image**, and **severe calorie restriction** leading to **low body weight** (BMI < 18.5 kg/m²).
  - Patients often fail to recognize the **seriousness** of their condition.

- **Subtypes**
  - **Restricting Type**: No binge eating or purging; weight loss achieved through dieting, exercise, or fasting.
  - **Binge-Eating/Purging Type**: Involves binge eating or purging (vomiting, laxative use, diuretics).
- **Features**
  - Significant low BMI (< 18.5 kg/m²).
  - Fear of weight gain, **distorted body image**.
  - Use of laxatives or other purgatives.
  - Lack of awareness of the seriousness of their condition.

- **Complications:** due to weight loss & malnutrition
  - **Endocrine:**
    - **Hypogonadism** → **Amenorrhea**, osteoporosis (↑ stress fractures).
    - Hypothyroidism, **Euthyroid sick syndrome**.
  - **Cardiac:**
    - Structural: ↓ cardiac mass, mitral valve prolapse, pericardial effusion.
    - Functional: **Bradycardia**, hypotension, QT prolongation (risk of dizziness).
  - **Refeeding Syndrome**: **Hypophosphatemia** → arrhythmias during nutritional rehabilitation.

- **Lab Findings**
  - Electrolyte imbalances: ↓ potassium, sodium, chloride, phosphate, magnesium.
  - Metabolic alkalosis (↑ bicarbonate).
  - ↑ Cortisol, growth hormone, glucose, cholesterol, carotene.
  - **Low T3**, normal T4/TSH.
  - Hypoalbuminemia.

- **Differential Diagnosis**
  - **Bulimia Nervosa:**
    - Normal or overweight BMI.
    - No severe calorie restriction or starvation complications seen in anorexia nervosa.
- **Treatment**
  - **First-Line:**
    - **Cognitive Behavioral Therapy (CBT).**
    - Nutritional support (monitor for refeeding syndrome).
  - **Second-Line:**
    - **Olanzapine** (antipsychotic) for severe cases.
    - Avoid **TCAs** (cardiotoxicity) and **bupropion** (seizure risk).
- **Key Points**
  - **Improvement**: Best marker is **weight gain of ~0.45 kg (1 lb) per week**.
  - Medications are not recommended as **sole treatment**.
  - Monitor for **refeeding syndrome** during nutritional rehabilitation.

Anorexia features
- most things low
- G's and C's raised: growth hormone, glucose, salivary glands, cortisol, cholesterol, carotinaemia

The best, most easily obtainable measure of clinical improvement in a patient with anorexia nervosa → a weight gain of 1 pound (0.45 kg) per week.

The antidepressant bupropion lowers the seizure threshold. It is, therefore, contraindicated in individuals with eating disorders who are at an increased risk of developing seizures secondary to dehydration and electrolyte imbalances.

Eating disorders

Bulimia nervosa

- **Definition**:
  - An eating disorder characterized by **binge eating** episodes followed by **compensatory behaviors** such as intentional vomiting to prevent weight gain.
- **Features**
  - **BMI**: Normal or slightly elevated (≥ 18.5 kg/m²).
  - **Russell sign**: Calluses on the dorsal hand from induced vomiting.
  - **Erosion of teeth, parotid gland hypertrophy.**
  - **Mallory-Weiss syndrome**: Esophageal tears from vomiting.
- **Lab findings**:
  - Electrolyte disturbances (e.g., ↓ potassium, ↓ chloride).
  - **Metabolic alkalosis.**
  - ↑ **Serum amylase** due to vomiting.
- **Treatment**
  - **First-line**: Cognitive Behavioral Therapy (CBT).
  - **Medication**: Not recommended as sole treatment.

Parotid hypertrophy and erosion of the teeth are the most common physical signs of Bulimia nervosa and may prompt diagnosis.

Eating disorders

Binge-Eating Disorder

- **Definition**
  - A type of eating disorder characterized by **recurrent episodes of binge eating** (eating a large amount of food in a short time) without compensatory behaviors like purging, excessive exercise, or fasting.
- **Features**
  - Episodes occur **at least once a week for 3 months.**
  - Associated with:
    - **Loss of control** during eating episodes.
    - **Distress** about binge eating.
    - Eating rapidly, when not hungry, until uncomfortably full, or eating alone due to embarrassment.
  - No compensatory behaviors (distinguishes it from bulimia nervosa).
- **Complications**
  - **Medical**:
    - **Obesity** and related comorbidities (e.g., diabetes, hypertension, hyperlipidemia).
    - Gastrointestinal issues (e.g., gastric dilation).
  - **Psychological**:
    - Guilt, shame, low self-esteem, depression, anxiety.

- **Diagnosis Criteria (DSM-5)**
  - Episodes of binge eating involve **three or more** of the following:
    - Eating more rapidly than normal.
    - Eating until uncomfortably full.
    - Eating large amounts when not hungry.
    - Eating alone due to embarrassment.
    - Feeling disgusted, depressed, or guilty afterward.

- **Treatment**
  - **First-Line Therapy**:
    - **Cognitive Behavioral Therapy (CBT)**: Effective in reducing binge episodes.
    - **Interpersonal Therapy (IPT)**: Targets relationship stressors contributing to binge eating.
  - **Medications**:
    - **Lisdexamfetamine** (FDA-approved): Reduces binge episodes.
    - **SSRIs**: Improve associated depression and reduce binge frequency.
    - **Topiramate**: May help with weight loss and binge reduction (off-label).
  - **Nutritional Counseling**:
    - Focus on structured eating patterns and portion control.

- **Key Points**
  - **Most common eating disorder**, often linked to **obesity**.
  - Focus on **psychological therapy** as first-line treatment.
  - Medications like **lisdexamfetamine** and **SSRIs** can help reduce binge frequency.

Antipsychotics

Types

1. **Typical Antipsychotics** (First-generation):
   - Primarily block **dopamine D2 receptors**.
   - Effective for **positive symptoms** (e.g., hallucinations, delusions).
   - Examples: **Haloperidol, Chlorpromazine, Thioridazine**.
   - Side effects: **Extrapyramidal symptoms (EPS)**, sedation, anticholinergic effects.
2. **Atypical Antipsychotics** (Second-generation):
   - Block **D2 receptors** and **5-HT2A receptors**.
   - Effective for **positive and negative symptoms**.
   - Examples: **Risperidone, Olanzapine, Quetiapine, Clozapine**.
   - Side effects: **Metabolic syndrome** (weight gain, diabetes), sedation.

> Antipsychotics in the elderly - increased risk of stroke and VTE

Typical Antipsychotics

Aspect	Details
Mechanism of Action	Inhibit **dopamine D2 receptors** in the mesolimbic pathway → decrease in positive symptoms of schizophrenia.
High-Potency Drugs	- **Haloperidol** - **Fluphenazine** - **Perphenazine**
Low-Potency Drugs	- **Chlorpromazine** - **Thioridazine**
Indications	- Schizophrenia (positive symptoms). - Acute psychosis. - Agitation. - Nausea/vomiting (e.g., haloperidol).
Side Effects	- **Extrapyramidal symptoms (EPS)**: Common in high-potency drugs. - **Anticholinergic effects**: Dry mouth, constipation, blurred vision. - **Cardiovascular**: Hypotension, QT prolongation (e.g., thioridazine). - **Other**: Sedation, weight gain. - **Chlorpromazine → Corneal deposits**: Brownish pigmentation of the cornea. - **Thioridazine → Retinal deposits**
Unique Features	- **Haloperidol**: Available as long-acting depot, can be used IM in acute situations. - **Chlorpromazine**: Associated with corneal deposits. - **Thioridazine**: Causes retinal deposits and QT prolongation.
Advantages	- Effective for **positive symptoms** of schizophrenia. - High-potency drugs cause **less sedation and hypotension**.
Disadvantages	- High risk of **EPS** (especially with high-potency agents). - Limited efficacy for **negative symptoms** of schizophrenia. - Toxic in overdose.
Key Notes	- **High-potency**: More EPS, less sedation (e.g., haloperidol). - **Low-potency**: More sedation and anticholinergic effects (e.g., chlorpromazine).

Atypical Antipsychotics

Aspect	Details
Definition	A class of antipsychotics that block **dopamine D2 receptors** and **serotonin 5-HT2A receptors**, used for schizophrenia and other psychiatric conditions.
Examples	- **Clozapine** - **Risperidone** - **Olanzapine** - **Quetiapine** - **Aripiprazole** - **Ziprasidone**

Aspect	Details
Mechanism of Action	- **Dopamine D2 receptor blockade**: Reduces positive symptoms of schizophrenia. - **5-HT2A receptor blockade**: Improves negative symptoms and reduces extrapyramidal side effects (EPS).
Indications	- **Schizophrenia** (first-line). - **Bipolar disorder** (mania, mixed episodes, and maintenance). - Treatment-resistant depression (adjunctive).
Side Effects	- **Metabolic syndrome**: Weight gain, hyperglycemia, dyslipidemia (common with clozapine, olanzapine). - **Extrapyramidal symptoms (EPS)**: Less common than typical antipsychotics. - **Sedation** (e.g., quetiapine, clozapine). - **QT prolongation** (e.g., ziprasidone). - **Agranulocytosis**: Specific to clozapine; requires regular blood monitoring.
Advantages	- Lower risk of EPS compared to typical antipsychotics. - Effective for both **positive** and **negative symptoms** of schizophrenia.
Contraindications	- Known hypersensitivity to the drug. - **Clozapine**: Contraindicated in patients with uncontrolled epilepsy, agranulocytosis, or severe cardiac disease.
Monitoring	- Regular monitoring for **metabolic syndrome** (weight, blood glucose, lipids). - **Clozapine**: Requires routine blood tests (ANC levels) to prevent agranulocytosis.
Key Notes	- **Aripiprazole**: Partial D2 agonist; lower risk of weight gain. - **Clozapine**: Reserved for treatment-resistant schizophrenia.

Atypical antipsychotics such as olanzapine/risperidone/clozapine → associated with weight gain, hyperglycaemia insulin resistance.

Clozapine:

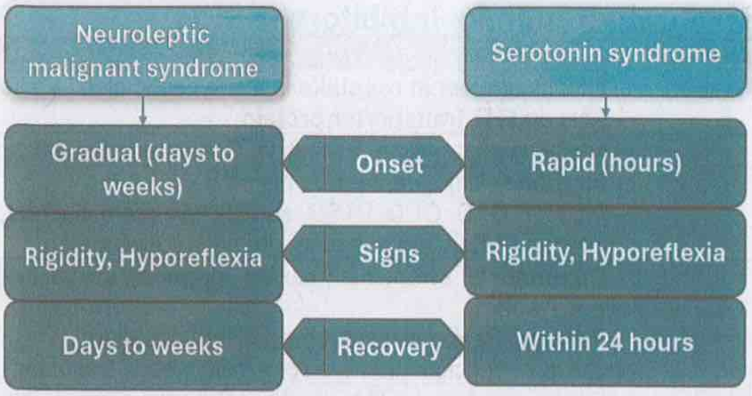
- **→ Decreased suicide risk**
- **→ Agranulocytosis (so not used as 1st line)**

Comparison: Neuroleptic Malignant Syndrome (NMS) vs. Serotonin Syndrome (SS)

Aspect	Neuroleptic Malignant Syndrome (NMS)	Serotonin Syndrome (SS)
Cause	- **Dopamine receptor blockade** due to antipsychotics (e.g., haloperidol).	- **Excess serotonin** from SSRIs, SNRIs, MAOIs, TCAs, or serotonergic drugs.
Onset	- Gradual onset (days to weeks after starting or increasing dose).	- Rapid onset (hours after starting or increasing dose).
Symptoms	- **Hyperthermia**, muscle rigidity ("lead-pipe"), altered mental status, autonomic dysfunction (e.g., hypertension, tachycardia).	- **Hyperthermia**, hyperreflexia, clonus (spontaneous/inducible), tremor, agitation, mydriasis.
Muscle Tone	- **Rigidity** (lead-pipe), hyporeflexia.	- **Increased tone** with **hyperreflexia** and clonus (hallmark feature).
Autonomic Instability	- Severe (e.g., tachycardia, labile blood pressure, diaphoresis).	- Severe (e.g., tachycardia, hypertension, hyperthermia, sweating).
Mental Status Changes	- Confusion, agitation, stupor, delirium.	- Anxiety, restlessness, agitation, confusion.
Causative Drugs	- **Antipsychotics** (e.g., haloperidol, chlorpromazine, risperidone). - Sudden withdrawal of dopamine agonists.	- **Serotonergic drugs** (SSRIs, SNRIs, MAOIs, TCAs, tramadol, MDMA).
Laboratory Findings	- ↑ Creatine kinase (CK), leukocytosis, metabolic acidosis.	- No specific findings, mild CK elevation, normal labs except serotonin toxicity.
Treatment	- **Stop antipsychotics**. - Supportive care: IV fluids, cooling, sedation. - **Dantrolene** (for rigidity) or **bromocriptine** (dopamine agonist).	- **Stop serotonergic drugs**. - Supportive care: IV fluids, cooling, sedation. - **Cyproheptadine** (serotonin antagonist).
Prognosis	- Recovery can take **days to weeks**.	- Recovery typically within **24–48 hours** with proper treatment.

NMS may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

A patient with P/H/O Parkinson's disease, deteriorate 1 – 2 days after admission to hospital for other condition → neuroleptic malignant syndrome (NMS) as a result of not taking her Parkinson's medication → Do Creatine kinase to confirm the diagnosis



Typical Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Examples**: Fluoxetine, Sertraline, Citalopram.
- **Action**: Inhibit serotonin reuptake.
- **Features**: First-line for depression and anxiety; side effects include nausea, insomnia, sexual dysfunction.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- **Examples**: Venlafaxine, Duloxetine.
- **Action**: Inhibit serotonin and norepinephrine reuptake.
- **Features**: Useful for depression with **pain symptoms**; side effects include hypertension, nausea.

Tricyclic Antidepressants (TCAs)

- **Examples**: Amitriptyline, Nortriptyline.
- **Action**: Inhibit serotonin and norepinephrine reuptake.
- **Features**: Older drugs; used for **neuropathic pain** and migraines. Side effects: sedation, weight gain, cardiotoxicity.

Monoamine Oxidase Inhibitors (MAOIs)

- **Examples**: Phenelzine, Tranylcypromine.
- **Action**: Inhibit monoamine oxidase, preventing breakdown of serotonin, norepinephrine, and dopamine.
- **Features**: Used in **treatment-resistant depression**; dietary restrictions (avoid tyramine); risk of hypertensive crisis.

Key Points

- **SSRIs/SNRIs**: Preferred due to safety and tolerability.
- **TCAs/MAOIs**: Effective but with more side effects and specific uses.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Aspect	Details
Mechanism of Action	- Inhibits **serotonin reuptake** in the synaptic cleft → ↑ serotonin levels. - Acts on **5HT transporter protein**.
Examples	Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram.
Indications	- **First-line**: Major depressive disorder. - Also for: GAD, OCD, PTSD, somatic symptom disorder, panic disorder, PMDD, binge-eating, premature ejaculation.
Side Effects	- **Common**: GI symptoms (nausea, diarrhea), sexual dysfunction, sleep issues. - **Serious**: Serotonin syndrome, QT prolongation (citalopram/escitalopram), suicide risk in early treatment.
Contraindications	- Concomitant use of **MAOIs, linezolid**, or methylene blue (risk of serotonin syndrome).
Special Considerations	- **Citalopram/Sertraline**: Preferred in chronic illness for fewer interactions. - Avoid **citalopram/escitalopram** in QT prolongation or long QT syndrome. - **Fluoxetine**: Preferred in children/adolescents.
Interactions	- Avoid with **NSAIDs** (co-prescribe PPI if used). - Avoid with **warfarin/heparin** (consider mirtazapine). - Avoid **triptans** (risk of serotonin syndrome).
Follow-Up	- Review at **2 weeks**; **1 week** for patients under 30 or high suicide risk. - Continue treatment for **6 months** after remission to reduce relapse risk.
Discontinuation	- Gradual taper over **4 weeks** (except fluoxetine due to long half-life). - **Paroxetine**: Higher risk of withdrawal symptoms. - **Symptoms**: Anxiety, mood lability, vivid dreams, dizziness, nausea.
Management in Alzheimer's	- **Citalopram** (≤20 mg): Best option; improves mood, agitation, and caregiver distress. - **Fluoxetine/sertraline**: Limited efficacy. - **Valproate**: Not effective in Alzheimer's.

SSRIs

- ⇨ **the first-line treatment for the vast majority of patients with depression**
- ⇨ **Risk of suicide attempt a few days after commencing treatment**
- ⇨ **citalopram & sertraline as these have a lower propensity for interactions (useful for people with chronic diseases). sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants**
- ⇨ **citalopram and escitalopram are associated with dose-dependent QT interval prolongation**
- ⇨ **triptans: avoid SSRIs**
- ⇨ **Paroxetine has a higher incidence of discontinuation symptoms.**

SSRI + NSAID = GI bleeding risk - give a PPI

Paroxetine - higher incidence of discontinuation symptoms

Selective Serotonin-Norepinephrine Reuptake Inhibitors (SSNRIs)

Aspect	Details
Mechanism of Action	Inhibits **serotonin** and **norepinephrine reuptake** in the synaptic cleft → increases serotonin and norepinephrine levels.
Drugs	Venlafaxine, Duloxetine.
Indications	- **Second-line** for major depressive disorder. - Generalized anxiety disorder. - Panic disorder. - Duloxetine: Stress incontinence in women.
Side Effects	- Similar to SSRIs (e.g., GI symptoms, sexual dysfunction). - **Increased blood pressure** (monitor before and during therapy).
Contraindications	- Risk of **serotonin syndrome** if used with **MAOIs**, linezolid, or methylene blue within 14 days.
Additional Notes	- **Blood pressure** should be controlled before starting therapy. - Effective for depression with physical symptoms like pain.

Serotonin Antagonist and Reuptake Inhibitors (SARIs)

Aspect	Details
Mechanism of Action	- Inhibits **serotonin reuptake** → increases serotonin levels. - Antagonist of **H1** and **α1-receptors**.
Drugs	Trazodone, Nefazodone.
Indications	- **Major depressive disorder**, especially in patients with insomnia. - Off-label: Insomnia without depression.
Side Effects	- **Priapism** (rare). - **Sedation** (H1 antagonism). - **Orthostatic hypotension**.
Contraindications	- Risk of **serotonin syndrome** if combined with **MAOIs**, linezolid, or methylene blue within 14 days.
Additional Notes	- Often used as an **adjunct** to other antidepressants for insomnia associated with depression. - Commonly prescribed for sleep issues.

Monoamine Oxidase Inhibitors (MAOIs)

Aspect	Details
Mechanism	- Inhibits **monoamine oxidase** → decreases breakdown of **epinephrine, norepinephrine, and serotonin** → increases their levels.
Drugs	- **Tranylcypromine** - **Phenelzine** - **Selegiline** (oral for Parkinson's, transdermal for depression) - **Isocarboxazid**
Indications	- **Major depressive disorder** (third- or fourth-line due to severe side effects). - Effective for **atypical depression** (e.g., ↑ appetite, sleep, leaden paralysis). - **Selegiline**: Parkinson's disease (adjunct to carbidopa-levodopa).
Side Effects	- **Hypertensive crisis**: Triggered by tyramine-rich foods (e.g., aged cheeses, smoked meats, alcohol, dried fruits). - **Serotonin syndrome** (if combined with serotonergic drugs).
Contraindications	- Risk of **serotonin syndrome** if combined with **MAOIs**, linezolid, or methylene blue within 14 days.
Additional Notes	- Requires **dietary restrictions** to avoid tyramine-related hypertensive crises. - Selegiline transdermal patch bypasses dietary restrictions at low doses.

Tricyclic Antidepressants (TCAs)

Aspect	Details
Mechanism of Action	Inhibits **serotonin** and **norepinephrine reuptake** in the synaptic cleft → increases levels of serotonin and norepinephrine.
Drugs	**Tertiary Amines**: Amitriptyline, Clomipramine, Doxepin, Imipramine, Trimipramine. **Secondary Amines**: Nortriptyline, Desipramine, Protriptyline.
Indications	- Less common for depression (due to side effects/toxicity). - **Neuropathic pain** (e.g., diabetic neuropathy). - Headache prophylaxis (tension, migraine). - Chronic pain (fibromyalgia). - Major depressive disorder (third- or fourth-line).
Side Effects	- **Orthostatic hypotension**. - **Sedation and delirium** (more with tertiary amines). - **Anticholinergic effects**: - **Cardiovascular**: Tachycardia, wide QRS, arrhythmias. - **CNS**: Confusion, seizures, coma. - **GI**: Ileus, constipation. - **General**: Xerostomia, blurred vision, hyperthermia.

Aspect	Details
Overdose	- **Lethality**: **Amitriptyline and dosulepin are most toxic in overdose**; **lofepramine is less toxic.** - **Clinical features**: Anticholinergic effects, arrhythmias, seizures. - **Management**: - Secure airway, fluid resuscitation. - **Activated charcoal** can be used within 2 hours of overdose ingestion. - **ECG**: Monitor for arrhythmias. - **Sodium bicarbonate**: For QRS prolongation/arrhythmias. - **Benzodiazepines**: For seizures. - Avoid physostigmine (risk of cardiac arrest).
Contraindications	- Risk of **serotonin syndrome** with **MAOIs**, linezolid, or methylene blue. - Avoid tertiary amines in the **elderly** due to confusion and sedation risks.
Additional Notes	- Rarely used as **first-line antidepressants** due to side effects and overdose risk. - **Antimuscarinic effects more common with imipramine.**

Dosulepin - avoid as dangerous in overdose

Lofepramine - the safest TCA in overdosage

Atypical antidepressants

Definition

- **Atypical antidepressants** are a group of medications that work differently from **typical (conventional) antidepressants** like SSRIs, SNRIs, tricyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs).
- They have **unique mechanisms of action** and are often used when first-line treatments are ineffective or not well-tolerated.

Mirtazapine

- **Mechanism of action**
  - ⇨ α_2-adrenergic antagonist → ↑ serotonin and norepinephrine release
  - ⇨ **$5\text{-}HT_2$ and $5\text{-}HT_3$ receptor antagonist → ↑ effect of serotonin on free $5\text{-}HT_1$ receptor → likely responsible for antidepressant effects**
  - ⇨ H_1 antagonist
- **Indications**
  - ⇨ major depressive disorder, especially in underweight and insomniac patients
- **Side effects**
  - ⇨ ↑ appetite and weight gain
  - ⇨ Sedation (due to H_1 antagonism)
- **Contraindications**
  - ⇨ risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

Bupropion

- **Mechanism of action**
  - ⇨ not fully understood, but thought to **increase dopamine and norepinephrine levels via reuptake inhibition**
- **Indications**
  - ⇨ Smoking cessation:
    - used in conjunction with counseling and nicotine replacement
  - ⇨ Major depressive disorder
  - ⇨ Depressive disorders with seasonal pattern
- **Side effects**
  - ⇨ **Reduction of seizure threshold**
  - ⇨ Tachycardia, palpitations, agitation
  - ⇨ Weight loss
  - ⇨ Neuropsychiatric symptoms (including depression, mania, psychosis, and paranoia)
- **Contraindications**
  - ⇨ Patients with ↑ risk for seizure (epilepsy, anorexia/bulimia, alcohol or benzodiazepine withdrawal, etc.)
  - ⇨ Risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
- **Additional information**
  - ⇨ Bupropion has **no sexual side effects**, which makes it a viable alternative to SSRIs or SSNRIs for patients who experience sexual dysfunction.

Benzodiazepines

Aspect	Details
Definition	Sedative-hypnotic medications enhancing **GABA-A receptor activity**, causing **CNS depression**.
Mechanism of Action	Increases **GABA-mediated inhibition** by enhancing chloride channel opening at GABA-A receptors.
Indications	- **Short-Term Use**: Anxiety, insomnia, acute agitation. - **Seizures**: Status epilepticus. - **Alcohol Withdrawal**: Prevent seizures/delirium tremens. - **Muscle Spasms**: Relief of spasticity. - **Procedural Sedation**: Preoperative or minor procedures.
Common Drugs	- **Diazepam**: Anxiety, alcohol withdrawal, seizures (**long half-life, >24 hours**). - **Lorazepam**: Anxiety, status epilepticus (**intermediate half-life, 10–20 hours**). - **Alprazolam**: Panic disorder (**intermediate half-life, 10–15 hours**). - **Clonazepam**: Seizures, panic disorder (**long half-life, 18–50 hours**). - **Midazolam**: Procedural sedation (**short half-life, <6 hours**). - **Oxazepam**: Alcohol withdrawal (**short half-life, 6–10 hours**).
Side Effects	- **Common**: Drowsiness, dizziness, muscle weakness, impaired coordination. - **Serious**: Dependence, tolerance, respiratory depression, cognitive impairment.

Aspect	Details
Precautions	- Use **short-term** only to avoid dependence/tolerance. - Avoid in: Respiratory conditions (e.g., COPD), substance misuse history, elderly (risk of falls/confusion).
Withdrawal	- **Symptoms**: Anxiety, tremors, insomnia, agitation, seizures. - **Management**: Gradual tapering over weeks/months.

Benzodiazepine Withdrawal

Aspect	Details
Withdrawal Protocol	- Reduce dose by **1/8** (range: 1/10 to 1/4) of daily dose every **fortnight**. - **Suggested protocol**: - Switch to an equivalent dose of **diazepam**. - Reduce diazepam dose by **2–2.5 mg every 2–3 weeks**. - Withdrawal duration: **1 month to >1 year**.
Withdrawal Syndrome	- Occurs if tapering is **too rapid**, resembling **alcohol withdrawal syndrome**. - Can occur **up to 3 weeks** after stopping long-acting benzodiazepines.
Symptoms of Withdrawal	- **Psychological**: Insomnia, anxiety, irritability. - **Physical**: Tremor, loss of appetite, tinnitus, perspiration. - **Severe**: Perceptual disturbances, seizures.

Flumazenil: Summary Notes

Aspect	Details
Mechanism of Action	- a **benzodiazepine antagonist** acts as a **competitive antagonist** at the GABA-A receptor benzodiazepine binding site. - Reverses sedation, respiratory depression, and other CNS effects caused by benzodiazepines.
Indications	- **Reversal of benzodiazepine sedation** (e.g., after procedural sedation). - **Management of benzodiazepine overdose** in certain cases. - Diagnostic use in benzodiazepine-induced coma or sedation.
Contraindications	- Patients with **benzodiazepine dependence** (can precipitate withdrawal, including seizures). - **Mixed drug overdoses** (e.g., with tricyclic antidepressants or other pro-convulsant agents).
Dosage and Administration	- **Initial dose**: 0.2 mg IV over 15 seconds. - If no response, repeat with 0.1 mg IV every 60 seconds (up to a max of 1 mg). - Continuous monitoring required during administration.
Adverse Effects	- **Common**: Nausea, vomiting, dizziness, agitation. - **Serious**: Precipitation of seizures in benzodiazepine-dependent patients or mixed overdoses.

Aspect	Details
Precautions	- Use cautiously in patients with **epilepsy**, **head injury**, or mixed-drug overdose. - Monitor for **re-sedation**, as flumazenil's half-life (0.7–1.3 hours) is shorter than most benzodiazepines.

$GABA_A$ drugs

- benzodiazipines increase the frequency of chloride channels
- barbiturates increase the duration of chloride channel opening

Frequently Bend - During Barbeque

...or...

Barbidurates increase duration & Frendodiazepines increase frequency

Benzodiazepines enhance the effect of GABA, the main inhibitory neurotransmitter

Lorazepam (half-life 10–20 hours) and oxazepam (half-life 6–10 hours) are considered safer in overdose due to their minimal liver metabolism and shorter half-life. Midazolam is short-acting (half-life, <6 hours) but is only used intravenously.

Post-Traumatic Stress Disorder (PTSD)

Definition

- PTSD can occur at any age after exposure to a **traumatic event** (e.g., disasters, abuse, war).
- Symptoms must persist for **>1 month** (DSM-IV criteria) and often have a delayed onset with a prolonged course.

Features

- **Re-experiencing**: Flashbacks, nightmares, intrusive distressing images.
- **Avoidance**: Avoiding people, situations, or reminders of the trauma.
- **Hyperarousal**: Hypervigilance, exaggerated startle response, sleep disturbances, irritability, difficulty concentrating.
- **Emotional Numbing**: Detachment, inability to feel emotions.
- **Associated Symptoms**: Depression, anger, drug/alcohol misuse, unexplained physical symptoms.

Management

- **Watchful waiting**: For mild symptoms lasting <4 weeks.
- **Psychological Interventions**:
  - **Trauma-focused CBT** or **Eye Movement Desensitisation and Reprocessing (EMDR)** for severe cases.
- **Pharmacological Treatment**:
  - **Not first-line.**
  - If used: **Paroxetine** or **Mirtazapine** recommended.

Comparison: Post-Traumatic Stress Disorder (PTSD) vs Post-Concussion Syndrome (PCS)

Aspect	Post-Traumatic Stress Disorder (PTSD)	Post-Concussion Syndrome (PCS)
Definition	A mental health condition that develops after exposure to a **traumatic event** (e.g., disaster, abuse, war).	A set of symptoms that persist after a **mild traumatic brain injury (TBI)** (e.g., head injury).
Cause	Psychological trauma from witnessing or experiencing life-threatening or distressing events.	Physical trauma to the head causing brain injury.
Onset	Symptoms usually begin **days to weeks** after the trauma but may be delayed.	Symptoms typically begin **immediately or within hours/days** after the head injury.
Core Symptoms	- **Re-experiencing**: Flashbacks, nightmares. - **Avoidance**: Avoiding reminders of the trauma. - **Hyperarousal**: Sleep issues, irritability, hypervigilance. - **Emotional numbing**: Detachment, lack of emotion.	- **Cognitive**: Headache, poor concentration, memory problems. - **Emotional**: Irritability, anxiety, depression. - **Physical**: Dizziness, fatigue, sensitivity to light/noise.
Duration	Symptoms must last **>1 month** to meet diagnostic criteria (DSM-5).	Symptoms usually resolve in **weeks to months**, but can persist >3 months in some cases (chronic PCS).
Diagnosis	Clinical diagnosis based on DSM-5 criteria: Requires trauma exposure and core symptoms lasting **≥1 month**.	Clinical diagnosis; **imaging (CT/MRI)** often normal. Rule out other causes of persistent symptoms.
Treatment	- **Psychological**: Trauma-focused CBT, EMDR. - **Pharmacological**: SSRIs (e.g., paroxetine), mirtazapine (if needed).	- **Rest and reassurance.** - Treat symptoms individually (e.g., analgesics for headache, CBT for emotional symptoms).
Prognosis	Can be chronic but improves with therapy; early intervention leads to better outcomes.	Usually resolves fully within months, but persistent symptoms can occur in severe cases.

Grief Reaction

Definition

- Grief is a **natural response to loss**, involving emotional, physical, and cognitive reactions. It becomes a concern when it transitions to **complicated grief** or significantly impairs daily functioning.

Types of Grief

1. **Normal Grief**:
    - Resolves over time without clinical intervention.
2. **Complicated Grief (Prolonged Grief Disorder)**:
    - **Intense, disabling grief** lasting **>6 months**, associated with functional impairment.
3. **Anticipatory Grief**:
    - Occurs before a loss, often in caregivers or families of terminally ill patients.

Symptoms of Grief

- **Emotional**: Sadness, anger, guilt, longing, or numbness.
- **Physical**: Fatigue, sleep disturbances, appetite changes.
- **Behavioural**: Social withdrawal, inability to focus, preoccupation with the deceased.

Phases of Grief

- **Shock and Denial**: Difficulty accepting the loss.
- **Pain and Guilt**: Emotional distress and self-blame.
- **Anger and Bargaining**: Frustration and attempts to find meaning.
- **Depression**: Sadness, loneliness, and withdrawal.
- **Acceptance and Adjustment**: Gradual return to normal functioning.

Management

- **Normal Grief**:
    - **Reassurance and Support**:
        - Acknowledge grief as a natural process.
        - Encourage **social connections** (family, friends, or support groups).
    - **Self-care**: Regular sleep, balanced diet, and physical activity.
- **Complicated Grief**: **Refer for Specialist**
    - **Referral Criteria**
        - Prolonged grief: Symptoms lasting >6 months.
        - Functional impairment and inability to adapt.
        - Coexisting mental health issues: Depression, PTSD, or substance abuse.
    - **Treatment**
        - **Cognitive Behavioural Therapy (CBT)** or grief-specific therapy.
        - **Medications** (antidepressants) if comorbid depression or anxiety exists.

Depression

Definition

- Depression is a **mental health condition** characterized by **persistent low mood, loss of interest**, and other emotional, cognitive, and physical symptoms that impair daily functioning.

Symptoms (DSM-5/ICD-10 Criteria)

- At least 5 of the following symptoms for ≥2 weeks:
  1. Persistent **low mood**.
  2. **Anhedonia** (loss of interest/pleasure).
  3. **Fatigue** or low energy.
  4. **Sleep disturbance** (insomnia or hypersomnia).
  5. Changes in **appetite/weight**.
  6. **Poor concentration** or indecisiveness.
  7. Feelings of **worthlessness** or guilt.
  8. **Psychomotor changes** (agitation or retardation).
  9. **Suicidal thoughts** or attempts.

Classification (Severity)

- **Mild**: Few symptoms with minor functional impairment.
- **Moderate**: Significant symptoms causing functional difficulty.
- **Severe**: Many symptoms causing marked functional impairment, potentially with **psychotic features** (e.g., delusions).

Assessment

- **Screening Tools**:
  - **Patient Health Questionnaire (PHQ-9)**: Measures severity of symptoms.
  - **GAD-7** (if anxiety is present).
- Exclude medical causes: Thyroid dysfunction, anemia, chronic illnesses.
- Assess for **suicide risk** and comorbidities.

Risk factors for suicide

- **Standard risk factors for suicide**
  - male sex
  - advancing age
  - unemployment or social isolation
  - divorced or widowed
  - history of mental illness (depression, schizophrenia)
  - history of deliberate self-harm
  - alcohol or drug misuse
- **Factors associated with risk of suicide following an episode of deliberate self-harm:**
  - efforts to avoid discovery
  - planning
  - leaving a written note
  - final acts such as sorting out finances
  - violent method

Management (Stepwise Approach by NICE)

1. **Mild Depression**:
   - **Low-intensity psychological interventions**:
     - Self-help programs.
     - Guided self-help.
     - Group-based CBT.
   - Active monitoring and regular follow-up.

2. **Moderate to Severe Depression**:
   - **High-intensity psychological therapies**:
     - Individual **CBT** or **interpersonal therapy (IPT)**.
   - **Antidepressants**:
     - **First-line**: SSRIs (e.g., sertraline, fluoxetine, citalopram).
     - Monitor young patients closely for increased suicide risk in the first month.
3. **Severe Depression with Psychosis**:
   - Combination of **antidepressants** and **antipsychotics**.
   - **Electroconvulsive Therapy (ECT)** for treatment-resistant or life-threatening depression.
4. **Persistent Depression**:
   - Consider **augmentation strategies**:
     - Add a second antidepressant or a mood stabilizer (e.g., lithium).

Special Considerations

- **Postnatal Depression**:
  - CBT as first-line therapy.
  - **Sertraline** and **paroxetine** are safe during breastfeeding.
- **Older Adults**:
  - Start with lower doses of medication and monitor for side effects.

Psychotic depression

- **Psychotic depression: severe depression accompanied by psychotic features is uncommon but important due to high risk of suicide.**
- **The history of low mood predating the psychotic symptoms, also the fact that the auditory hallucinations and delusions are consistent with the depressive feelings of guilt, distinguish this from schizophrenia.**

Depressive pseudodementia

- **Short-term memory loss may occur in conjunction with depression (depressive pseudodementia) as well as being seen in dementia.**
- **The memory loss improves with treatment of the depression.**

Early morning waking is a classic somatic symptom of depression and often develops earlier than general insomnia.

A suicidal patient became agitated and insisted that she wanted to go home immediately. How should you proceed?

- **Call the duty psychiatrist, and with other staff in the Emergency Department attempt to restrain her until they arrive**
- **If the patient attempt to abscond before or during psychiatric assessment, the staff of the Emergency Department have a duty under Common Law to restrain the patient**

Generalised Anxiety Disorder (GAD)

Definition

- A chronic mental health condition characterized by **excessive and uncontrollable worry** about everyday events, lasting **≥6 months**.
- Characterized by disproportionate fear and anxiety.

Neurotransmitter changes in GAD

- Decreased GABA and serotonin levels.
- Increased norepinephrine.

Symptoms

- **Psychological**:
  - Persistent worry (out of proportion to actual events).
  - Difficulty controlling worry.
  - Irritability and poor concentration.
- **Physical**:
  - Fatigue, muscle tension, restlessness.
  - Sleep disturbances (difficulty falling or staying asleep).

Diagnosis

- **Rule out physical causes** such as: hyperthyroidism, cardiac disease, or medication-induced anxiety (e.g., salbutamol, theophylline, corticosteroids, caffeine).
- Based on **DSM-5 criteria**:
  - Excessive worry for ≥6 months.
  - Associated with ≥3 symptoms (e.g., restlessness, fatigue, tension).
  - Causes significant distress or impairment.

Management

1. **Psychotherapy**:
   - **Cognitive Behavioural Therapy (CBT)**: Gold standard for treatment.
2. **Pharmacotherapy**:
   - **First-line**: SSRIs (e.g., sertraline, escitalopram).
   - **Alternatives** (if SSRIs are not tolerated): SNRIs (e.g., venlafaxine).
   - **Short-term relief**: Benzodiazepines (limited use due to dependency risk).
   - Beta-blockers: For physical symptoms like palpitations.
3. **Lifestyle Modifications**:
   - Regular exercise, relaxation techniques, and good sleep hygiene.

Key Points

- GAD involves **persistent worry** impacting daily functioning.
- Treatment includes **CBT** and **SSRIs**, with lifestyle changes to improve outcomes.

SSRIs are the first-line pharmacological therapy for generalised anxiety disorder

Hyperventilation Syndrome (HVS)

Definition
- A condition of **rapid or deep breathing**, leading to **low CO2 levels** and physical symptoms, often triggered by **stress or anxiety**.

Symptoms
- **Physical**: Chest pain, tingling, dizziness, palpitations, breathlessness.
- **Psychological**: Anxiety, fear, sense of doom.

Diagnosis
- **Nijmegen Questionnaire**: Score >23/64 indicates HVS.
- Rule out medical causes (e.g., asthma, cardiac issues).

Management
- **Acute**:
  - Reassure the patient and encourage **controlled breathing**.
- **Long-term**:
  - **CBT** and breathing retraining.
  - Stress reduction and avoidance of stimulants.

Mood Disorders

Definition
- Mood disorders involve persistent disturbances in mood, ranging from **depression** to **mania**.

Types
1. **Depressive Disorders**:
   - **Major Depressive Disorder (MDD)**: Persistent low mood, anhedonia, fatigue, and impaired functioning.
   - **Dysthymia (Persistent Depressive Disorder)**: Chronic, milder depressive symptoms lasting ≥2 years.
2. **Bipolar Disorders**:
   - **Bipolar I**: Episodes of **mania** and depression.
   - **Bipolar II**: Episodes of **hypomania** and depression.
   - **Cyclothymia**: Chronic mood instability with milder highs and lows.

Symptoms
- **Depression**:
  - Low mood, anhedonia, fatigue, poor concentration, sleep/appetite changes.
- **Mania**:
  - Elevated mood, hyperactivity, grandiosity, reduced need for sleep, impulsivity.

Diagnosis
- Based on **DSM-5 criteria**:
  - Duration and severity of mood episodes.
  - Impacts on functioning.

Management
1. **Depressive Disorders**:
   - **Psychotherapy**: CBT, interpersonal therapy.
   - **Pharmacotherapy**: SSRIs, SNRIs, tricyclics.

2. **Bipolar Disorders**:
   - **Mood Stabilizers**: Lithium, valproate.
   - **Antipsychotics**: Quetiapine, olanzapine.
   - **CBT** and psychoeducation.

Bipolar I disorder
- **severe alterations in mood (mania and depression) that are usually episodic and recurrent.**

Bipolar II disorder
- characterised by one or more major **depressive** episodes, at least one **hypomanic** episode and NO manic episodes.

Hypomania vs mania

The presence of psychotic symptoms differentiates mania from hypomania		
Mania ⇨ Psychotic symptoms	**Mania and Hypomania**	
delusions of grandeur	**Mood**	**Predominately elevated irritable**
Auditory hallucinations	**Speech & Thought**	▪ **Pressured** ▪ **Flight of ideas** ▪ **Poor attention**
	Behaviour	▪ **Insomnia** ▪ **Loss of inhibitions: risk-taking** ▪ **Increased appetite**

Cognitive Behavioural Therapy (CBT)

Definition
- Cognitive Behavioural Therapy (CBT) is a structured, time-limited form of **psychotherapy** that aims to address dysfunctional thoughts and behaviours by helping individuals identify and challenge **negative thought patterns** and develop **coping strategies**.

Key Principles

1. **Cognitive Component**:
   - Identifies and challenges **distorted thinking** (e.g., catastrophizing, overgeneralizing).
   - Helps reframe thoughts to be more realistic and constructive.
2. **Behavioural Component**:
   - Focuses on modifying maladaptive behaviours through techniques like **exposure therapy**, **activity scheduling**, and **problem-solving**.

Indications

- **Mood Disorders**:
  - Depression.
  - Bipolar disorder (adjunct to medication).
- **Anxiety Disorders**:
  - Generalized anxiety disorder (GAD).
  - Panic disorder.
  - Social anxiety disorder.
  - Phobias.

- **Obsessive-Compulsive Disorder (OCD)**:
  - Exposure and response prevention (ERP) as a CBT strategy.
- **Post-Traumatic Stress Disorder (PTSD).**
- **Eating Disorders**:
  - Anorexia nervosa, bulimia, and binge eating disorder.
- **Substance Use Disorders**:
  - Reduces cravings and identifies triggers.
- **Psychosis**:
  - Helps address delusions and hallucinations.
- **Chronic Pain**:
  - Manages the psychological impact of pain.

Core Techniques

1. **Cognitive Restructuring**:
   - Identifying automatic negative thoughts and replacing them with balanced thoughts.
2. **Behavioural Activation**:
   - Encouraging engagement in pleasurable or meaningful activities to counteract inactivity.
3. **Exposure Therapy**:
   - Gradual exposure to feared situations to reduce avoidance and desensitize anxiety.
4. **Problem-Solving**:
   - Teaching practical skills for addressing life challenges.
5. **Relaxation Techniques**:
   - Breathing exercises, mindfulness, or progressive muscle relaxation.

Format

- **Duration**:
  - Typically 6–20 sessions depending on the condition.
- **Delivery**:
  - **Individual therapy**: One-on-one with a therapist.
  - **Group therapy**: Shared experiences and support.
  - **Self-help**: Books or online CBT modules.

Effectiveness

- CBT is supported by strong evidence for effectiveness across multiple conditions.
- Benefits are comparable to or better than medication in certain disorders (e.g., mild to moderate depression, anxiety).

Advantages

- Empowers individuals to become their own **therapist**.
- Focuses on **skills development** for long-term improvement.
- Non-invasive and suitable for a variety of conditions.

Seasonal affective disorder (SAD)

Definition

- depression which occurs predominately around the winter months.

Aetiology

- thought to be related to melatonin metabolism and changes during winter

Features

- Symptoms of hyperphagia, hypersomnia and weight gain are more typical in SAD compared with matched non-seasonal controls.

Treatment

- Bright light therapy has been shown to be more effective than placebo for patients with SAD
  (exposing individuals to bright light for several hours a day)

Body Dysmorphic Disorder (BDD)

Definition

- Body Dysmorphic Disorder (BDD) is a **mental health condition** characterized by an **excessive preoccupation** with one or more perceived defects or flaws in physical appearance that are **not observable** or appear **insignificant** to others.

Key features

1. **Preoccupation**:
   - Persistent focus on perceived flaws, such as skin imperfections, body size, facial features, or hair.
   - Causes significant distress or functional impairment.
2. **Compulsive Behaviours**:
   - Frequent checking in mirrors or avoiding mirrors.
   - Excessive grooming, skin picking, or seeking reassurance.
   - Camouflaging perceived flaws with makeup, clothing, or posture.
3. **Impact**:
   - Avoidance of social situations or public exposure.
   - Functional impairments in work, school, or relationships.
   - High rates of comorbid **depression**, **anxiety**, and **obsessive-compulsive disorder (OCD)**.

Epidemiology

- Prevalence: ~2% in the general population.
- Onset: Usually in adolescence or early adulthood.
- Equal occurrence in males and females, but the focus of concern may differ:
  - Males: Muscle dysmorphia, genitals, or hair.
  - Females: Skin, weight, or facial features.

Associated Conditions

- **Muscle Dysmorphia**:
  - A subtype where individuals are preoccupied with insufficient muscularity or body size.
- **Eating Disorders**:
  - Often co-occurs with conditions like anorexia or bulimia nervosa.
- **Substance Use Disorders**:
  - Use of anabolic steroids or other substances to alter appearance.

Diagnosis (DSM-5 Criteria)

1. **Preoccupation** with perceived physical flaws.
2. **Repetitive behaviours** or mental acts in response to the concerns.
3. Significant **distress or impairment** in functioning.
4. Symptoms are **not better explained** by an eating disorder or other mental health condition.

Management

- **Psychotherapy**:
  - **Cognitive Behavioural Therapy (CBT)**:
    - Focuses on challenging distorted beliefs and reducing compulsive behaviours.
  - **Exposure and Response Prevention (ERP)**:
    - Helps reduce avoidance and compulsive behaviours.
- **Pharmacotherapy**:
  - **Selective Serotonin Reuptake Inhibitors (SSRIs)**:
    - E.g., fluoxetine, sertraline; effective in reducing obsessive thoughts.
  - Higher doses may be required compared to depression.

Post-Partum Mental Health Problems

Definition

- Post-partum mental health problems refer to a spectrum of psychological and emotional disorders that occur after childbirth, ranging from mild mood disturbances to severe psychiatric conditions. These include:
  - **Baby-blues:** A transient and self-limiting mood disturbance characterized by tearfulness, irritability, and anxiety, typically seen within the first week after delivery.
  - **Postnatal depression:** A form of clinical depression occurring within the first-year post-partum, with symptoms such as low mood, fatigue, and anhedonia.
  - **Puerperal psychosis:** A rare but severe psychiatric condition with symptoms of delusions, hallucinations, and mood swings, usually manifesting within the first 2–3 weeks after delivery.

Types

Condition	Incidence	Onset	Features	Management
Baby-blues	60–70% of women	3–7 days post-birth, common in primips.	Anxiety, tearfulness, irritability.	**Reassurance and support**. The health visitor plays a key role.
Postnatal depression	~10% of women	Within 1 month, peaks at 3 months.	Features similar to **general depression**: low mood, anhedonia, poor concentration, fatigue.	**Reassurance and support**. CBT may help. SSRIs (**sertraline, paroxetine**) for severe cases if needed.
Puerperal psychosis	~0.2% of women	Within 2–3 weeks post-birth.	Severe **mood swings** (like bipolar disorder), **disordered perception** (e.g., auditory hallucinations).	Requires **hospital admission**. Recurrence risk ~20% in future pregnancies.

Key Notes

- **SSRIs** in severe postnatal depression:
  - **Paroxetine** preferred (low milk/plasma ratio).
  - **Fluoxetine** avoided due to a long half-life.
- **Puerperal psychosis** requires immediate intervention and hospitalization.

> Post-natal depression is seen in around 10% of women

Alcohol - Problem Drinking: Management

Screening tools

- **AUDIT (Alcohol Use Disorders Identification Test)**: Assesses quantity, frequency, and consequences of drinking.
- **CAGE Questionnaire**: Quick screening for alcohol problems.

Interventions

- **For mild to moderate problem drinking:**
  - **Motivational interviewing**:
    - Explore the risks of alcohol use.
    - Set realistic goals for reduction or cessation.
  - Promote **low-risk drinking guidelines**:
    - ≤14 units per week, spread over 3+ days (UK guidelines).
- **Psychosocial interventions**
  - **Cognitive Behavioural Therapy (CBT)**: Addresses thought patterns and behaviours contributing to alcohol use.
  - **Motivational Enhancement Therapy (MET)**:
  - Helps resolve ambivalence about stopping or reducing drinking.
  - **Family and Couple Therapy**: Addresses relational issues impacted by drinking.

- **Pharmacological treatments**:
  - **Disulfiram**:
    - **Causes an aversive reaction to alcohol.**
    - **Contraindicated** in severe cardiac disease and pregnancy.
  - **Acamprosate**:
    - **Reduces craving and maintains abstinence.**
    - Dose: 666 mg three times daily (adjust for renal impairment).
  - **Naltrexone**:
    - **Reduces alcohol cravings and the rewarding effects of alcohol.**
    - Dose: 50 mg daily.
  - **Topiramate**:
    - Off-label use to reduce cravings and heavy drinking.
- **Thiamine supplementation**:
  - To prevent **Wernicke's encephalopathy** in heavy drinkers.
- **Detoxification (if dependent)**
  - **Outpatient** for mild dependence: Benzodiazepines (e.g., **chlordiazepoxide** or **diazepam**) for withdrawal symptoms.
  - **Inpatient** for severe dependence or high-risk cases: Close monitoring for complications (e.g., **delirium tremens**, seizures).

Alcohol is a common cause of hypoglycaemia

Alcohol Withdrawal

Key Overview

- **Alcohol withdrawal** is the most common cause of **paranoid psychosis with visual hallucinations.**
- **Mechanism:**
  - **Chronic alcohol use:**
    - Enhances **GABA-mediated inhibition**.
    - Inhibits **NMDA glutamate receptors**.
  - **Alcohol withdrawal:**
    - **Decreases GABA** activity.
    - **Increases NMDA glutamate** transmission, leading to excitatory overactivity.

Timeline and Features

Time Since Last Drink	Features
6–12 hours	Minor withdrawal: Insomnia, tremor, anxiety, nausea, headache, sweating, palpitations.
12–24 hours	**Alcoholic hallucinosis**: Visual, auditory, and tactile hallucinations.
24–48 hours	**Withdrawal seizures**: Generalized tonic-clonic seizures.
48–72 hours	**Delirium tremens**: Severe symptoms with disorientation, hallucinations, agitation, and autonomic instability.

Specific Features

- **Minor Withdrawal**:
  - Early symptoms: **Tremor, insomnia, anxiety, nausea**, and **sweating**.
- **Withdrawal Seizures**:
  - Generalized **tonic-clonic seizures**.
  - Usually single or a few fits resolving within **6–12 hours**.
  - Focal seizures, prolonged postictal phase, or status epilepticus suggests another diagnosis.
  - 30% progress to **delirium tremens**.
- **Alcoholic Hallucinosis**:
  - Onset: **12–24 hours**.
  - **Visual, auditory, and tactile hallucinations** without confusion.
- **Delirium Tremens**:
  - Onset: **3–7 days** post-cessation.
  - Severe withdrawal symptoms:
    - **Visual hallucinations, autonomic instability** (tachycardia, hypertension, pyrexia).
    - Confusion, obtundation, sweating, agitation, and tremors.

Management

- **Benzodiazepines**:
  - First-line for alcohol withdrawal symptoms.
  - Short half-life benzodiazepines **(lorazepam, oxazepam)** preferred in hepatic impairment.
- **Carbamazepine**:
  - Effective alternative; starting dose: **800 mg/24 hours**.
- **Phenytoin**:
  - Avoided for alcohol withdrawal seizures due to **ineffectiveness** and risk of **hypotension**.
- **Thiamine**:
  - Essential for chronic alcohol use to prevent **Wernicke's encephalopathy**, but not immediately critical in acute withdrawal.

Alcohol withdrawal is the most common cause of paranoid psychosis with visual hallucination

In hepatic impairment benzodiazepines with a shorter half-life (e.g. lorazepam and oxazepam) are preferred

Psychosis

Definition

- **Psychosis** is a syndrome characterized by significant alterations in perception, thoughts, mood, and behaviour. **Schizophrenia** is the most common psychotic disorder, characterized by chronic or recurrent psychotic episodes.

Signs and Symptoms

1. **Positive Symptoms** (excess of normal function):
    - Disorganized behaviour, speech, or thoughts.
    - **Delusions**: Fixed, falsely-held beliefs.
    - **Hallucinations**: Sensory perceptions without external stimuli.
2. **Negative Symptoms** (deficit of normal function):
    - Emotional blunting, reduced speech, loss of motivation.
    - Self-neglect, social withdrawal.
3. **Prodromal Symptoms**:
    - Emotional disturbance, distress, or social functioning decline.
    - Transient or attenuated psychotic symptoms.
    - Suspicion, mistrust, or perceptual changes.

Causes

- **Primary psychotic disorders** (e.g., schizophrenia).
- **Secondary causes**:
    - Medications, substance misuse, or medical conditions (e.g., sepsis).

Complications

- **Premature death**: Increased risk of suicide, cardiovascular disease, and type 2 diabetes.
- Difficulties in **social functioning** and **substance misuse**.

Management

- **Initial assessment and referral**:
    - Assess for **risk of harm** to self or others:
        - **High risk**: Same-day referral to the **early intervention in psychosis service** or **crisis resolution and home treatment team**.
        - **Low risk**: Referral to the early intervention in psychosis service or specialist mental health service.
    - For suspected **prodromal phase**, refer to early intervention or specialist services.
    - **Antipsychotics should not be started** until assessed, unless advised by a psychiatrist.
- **Treatment**:
    - **Antipsychotic therapy**
        - Antipsychotics are the first-line treatment for most cases of psychosis, except for:
            - **Stimulant-related psychosis**.
            - **Catatonia** (requires specific treatment before antipsychotics).
        - Second-generation antipsychotics (e.g., **aripiprazole**, **risperidone**) are preferred due to fewer side effects.

- **Symptom-Specific Treatment**
  - **Agitation**:
    - Sedation or physical restraint may be required for severely agitated patients.
    - Sedating antipsychotics like **olanzapine** (5–10 mg orally/IM) or **haloperidol** (2–10 mg orally/IM).
    - Severe agitation: Combine antipsychotics with **lorazepam**.
    - For agitated patients refusing oral medication: Administer IM or IV antipsychotics.
  - **Insomnia**:
    - Use sedating antipsychotics like **quetiapine** (25 mg twice daily, target 300–400 mg nightly).
- **Cognitive Behavioural Therapy (CBT) with or without family intervention.**

Schizophrenia

Definition

- Schizophrenia is a **chronic psychiatric disorder** characterized by **psychosis**, disorganized thinking, emotional dysregulation, and functional impairment.

Epidemiology

- **Prevalence**: ~1% worldwide.
- **Onset**:
  - Men: Typically late teens to early 20s.
  - Women: Typically mid-20s to early 30s.

Risk factors

- **Family history** (genetic predisposition): lifetime risk of developing schizophrenia:
  - Monozygotic twin with schizophrenia: **50%**.
  - Parent with schizophrenia: **10–15%**.
  - Sibling with schizophrenia: **10%**.
  - No family history: **1%**.
- Obstetric complications (e.g., hypoxia, preterm birth).
- Substance use (e.g., cannabis, amphetamines).
- More common in **social classes IV and V**.
- Psychosocial stress.

Pathophysiology

- **Neurochemical**:
  - Hyperactivity of the **dopaminergic pathways** (positive symptoms).
  - Dysregulation of **glutamate and GABA** systems.
- **Structural brain abnormalities**:
  - Enlarged ventricles, cortical thinning, and reduced hippocampal volume.

Clinical Features

- **Positive Symptoms** (excess of normal function):
  - **Delusions**: Fixed false beliefs (e.g., persecutory, grandiose).
  - **Hallucinations**: Typically **auditory** (hearing voices).
  - Disorganized speech: Incoherence, tangentiality.
  - Disorganized or catatonic behavior.

- **Negative Symptoms** (deficit of normal function):
    - **Avolition**: Lack of motivation.
    - **Anhedonia**: Inability to experience pleasure.
    - **Alogia**: Reduced speech output.
    - **Affective flattening**: Diminished emotional expression.
    - Social withdrawal.
- **Cognitive Symptoms**:
    - Impaired executive function (e.g., planning, problem-solving).
    - Poor attention and memory.

Diagnosis

- Based on **DSM-5 criteria**:
    1. **At least 2 of the following symptoms** (≥1 must be from the first three):
        - Delusions.
        - Hallucinations.
        - Disorganized speech.
        - Grossly disorganized or catatonic behavior.
        - Negative symptoms.
    2. Symptoms must persist for **≥6 months**, including at least **1 month of active symptoms**.
    3. Significant impairment in **functioning**.
    4. Rule out **substance use** or medical conditions.

Differential Diagnosis

- **Schizoaffective disorder**: Features of both schizophrenia and mood disorders.
- **Delusional disorder**: Presence of delusions without other symptoms.
- **Bipolar disorder with psychotic features**.
- **Substance-induced psychosis**.
- **Neurological conditions** (e.g., epilepsy, brain tumor).

Treatment

- **Pharmacological**:
    - **Antipsychotics**:
        - First-generation (typical): **Haloperidol, chlorpromazine**.
        - Second-generation (atypical): **Risperidone**, **olanzapine**, **aripiprazole**.
            - Preferred due to fewer extrapyramidal side effects.
    - **Adjunctive therapies**:
        - Mood stabilizers or antidepressants for comorbid conditions.
        - Benzodiazepines for agitation or insomnia.
- **Non-Pharmacological**:
    - **Cognitive-behavioral therapy (CBT)**: Targets delusions and hallucinations.
    - **Family therapy**: Improves family dynamics and reduces relapse.
    - **Social skills training**: Enhances interpersonal functioning.
    - **Supported employment and housing**.
- **Electroconvulsive Therapy (ECT)**:
    - Reserved for treatment-resistant schizophrenia or catatonia.

Prognosis

- **Chronic course** with episodic relapses.
- Factors indicating **better prognosis:** Acute onset, good premorbid functioning, female gender.
- **Factors indicating poor prognosis:**
  - strong family history
  - gradual onset
  - low IQ
  - premorbid history of social withdrawal
  - lack of obvious precipitant
  - predominant negative symptoms
  - poor response to treatment.

Concrete thinking where a patient cannot use abstraction to understand the meaning of a sentence. It is more common in schizophrenia.

Electroconvulsive therapy (ECT)

Definition

- Electroconvulsive therapy (ECT) is a **medical treatment** that uses controlled electrical stimulation of the brain to induce a **generalized seizure** under **anaesthesia** and **muscle relaxation**.

Indications

- **life-threatening depressive stupor**, especially when a patient is refusing to eat and drink.
  - This is used as it generally has a shorter onset of action than antidepressant medication, which takes 2–3 weeks to work.
- severe depression refractory to medication
- psychotic symptoms.

Contraindications

- **Raised intracranial pressure**
- **Recent cerebrovascular accident**
  - Most guidelines state that a recent CVA (within 1 to 3 months) is a contraindication.

Side-effects

- **Short-term side-effects**
  - headache
  - nausea
  - short term memory impairment
  - memory loss of events prior to ECT
  - cardiac arrhythmia
- **Long-term side-effects**
  - some patients report impaired memory

Personality Disorders

Types of Personality Disorders

1. **Antisocial**:
    - Disregard for social norms, repeated unlawful acts.
    - Deceptive, impulsive, aggressive, and irresponsible.
    - Lacks remorse for mistreatment of others.
2. **Avoidant**:
    - Avoids social interactions due to fear of criticism or rejection.
    - Feels inferior, socially isolated but craves connection.
    - Restrains intimacy due to fear of ridicule.
3. **Borderline**:
    - Unstable relationships, self-image, and emotions.
    - Impulsivity in self-damaging areas (e.g., spending, substance abuse).
    - Recurrent suicidal behavior, chronic emptiness, intense anger.
    - Quasi-psychotic thoughts and fear of abandonment.
4. **Dependent**:
    - Excessive reliance on others for decision-making and care.
    - Fears abandonment and urgently seeks new relationships for support.
    - Difficulty expressing disagreement, lacks initiative.
5. **Histrionic**:
    - Overly dramatic, needs to be the center of attention.
    - Inappropriate sexual behavior, shallow emotions.
    - Uses appearance for attention and has impressionistic speech.
6. **Narcissistic**:
    - Grandiosity, entitlement, and excessive need for admiration.
    - Lacks empathy, exploits others for personal gain.
    - Arrogant, envious, and preoccupied with success or beauty.
7. **Obsessive-Compulsive**:
    - Perfectionism, excessive focus on rules, order, and morality.
    - Rigid, stingy, and struggles to delegate tasks.
    - Best managed with **CBT** and **Exposure Response Prevention (ERP)**.
8. **Paranoid**:
    - Hypersensitive, distrustful, and preoccupied with conspiracies.
    - Reluctant to confide, perceives attacks on character.
9. **Schizoid**:
    - Prefers solitude, emotionally detached, lacks close relationships.
    - Indifferent to praise, criticism, or social interactions.
10. **Schizotypal**:
    - Odd beliefs, magical thinking, and eccentric behavior.
    - Paranoid ideation, unusual perceptual disturbances.
    - Few close relationships, inappropriate affect, and odd speech.

Panic disorder

Definition

- Recurrent spontaneous attacks of intense fear and discomfort without an obvious cause or trigger.

Epidemiology

- **Prevalence**: Affects **2-6%** of adults.
- Women are **2-3 times more likely** to be affected.
- Commonly develops between **18-45 years**.

Risk Factors: **Asthma** increases risk by **4.5 times**.

Pathophysiology:

- Abnormal discharge from the **locus caeruleus** (the origin of most brain noradrenergic pathways) **in the midbrain has been implicated in panic attacks,** leading to **sympathetic overdrive.**
- Has a genetic component: **43% heritability** observed in first-degree relatives.

Features

- Attacks peak within **10 minutes** and last **20-30 minutes**.
  - **Intense fear of dying**, discomfort.
  - **Sympathetic overdrive**: Palpitations, sweating, tremors, hyperventilation.
  - **Other symptoms**: Chest pain, nausea, lightheadedness, chills, **choking**, **feeling of suffocation,** paresthesias, and disconnectedness.

Diagnosis

- **Rule out physical causes**
  - **ECG**: Rule out ischemia, infarction, or pericarditis.
  - **Thyroid function tests (TSH, T3, T4)**: Rule out hyperthyroidism.
  - **Urine toxicology**: Screen for stimulant or substance use.
- ≥4 panic attacks in 4 weeks or ≥1 panic attack followed by **≥1 month of fear** of recurrence.

Treatment

- **Cognitive-Behavioral Therapy (CBT)**: **First-line treatment** for all patients.
- **Benzodiazepines** (e.g., alprazolam, clonazepam): Emergency/urgent use for confidence-building.
- **Selective Serotonin Reuptake Inhibitors (SSRIs)** (e.g., escitalopram, sertraline): first-line for long-term pharmacological management.

> **Recurrent sudden attacks of intense anxiety or fear accompanied by physical symptoms (e.g: palpitations and a feeling of suffocation) without an obvious cause or trigger.**

Acute Confusional State (Delirium)

Definition

- Also known as **delirium** or **acute organic brain syndrome**.
- Sudden change in **mental state** or behaviour that is out of character, typically occurring within **hours to days**.

Risk Factors

- **Older age** (≥65 years): Affects up to **30% of elderly** hospitalised patients.
- **Cognitive impairment or dementia.**
- **Severe illness**:
  - 20–30% of medical ward patients develop delirium.
  - 10–50% of post-surgical patients develop delirium.
- **Current hip fracture.**

Features

- **Memory disturbances**: Short-term memory is more affected than long-term memory.
- **Behavioural changes**:
  - Agitation or withdrawal.
  - Disorientation and mood changes.
- **Hallucinations**: Often **visual**.
- **Disturbed sleep cycle.**
- **Poor attention.**

Diagnosis

- Based on clinical assessment using:
  - **DSM-IV criteria** or the **short Confusion Assessment Method (short CAM)**.
  - For critical care or post-surgery, use **CAM-ICU**.
- Differentiation:
  - **Delirium vs Dementia**:
    - **Delirium**: Sudden onset, potentially reversible.
    - **Dementia**: Gradual onset, progressive, chronic condition.
    - When in doubt, manage as **delirium** initially.

Treatment

1. **Non-Pharmacological**:
   - First-line intervention: Reassure patient, take history, assess mental state.
   - Modify the **environment** to reduce distress.
   - Avoid antipsychotics unless communication and de-escalation fail.
2. **Pharmacological**:
   - **Treat underlying cause** (e.g., infections, metabolic disturbances).
   - **Sedation**:
     - Use only as a **last resort** after identifying the cause.
     - **First-line drugs**:
       - **Haloperidol**: 0.5 mg orally (short-term, ≤1 week).
       - **Olanzapine**: Alternative to haloperidol.
     - **Mirtazapine**:
       - Enhances **noradrenergic and serotonergic transmission**.
       - Suitable for **thin, agitated elderly patients** due to its sedative and weight-gaining properties.
   - **Contraindications**:
     - Avoid antipsychotics in patients with **Parkinson's disease** or **dementia with Lewy bodies**.

Delusions

Definition

- **Delusion**: A **fixed, false belief** that is not consistent with cultural, educational, or societal norms and is maintained despite clear evidence to the contrary.

Types of Delusions

1. **Persecutory**:
   - Belief of being **harmed, harassed, or conspired against** by others.
   - Most common type in psychotic disorders.
2. **Grandiose**:
   - Belief in having **special powers, abilities, or importance**.
   - Example: Thinking one is a historical figure or has unique talents.
3. **Referential**:
   - Belief that ordinary events, objects, or people have **special meaning** or are directed at the person.
   - Example: Believing TV shows are sending personal messages.
4. **Erotomanic**:
   - Belief that another person, often of higher status, is **in love** with them.
5. **Somatic**:
   - False beliefs about the **body or physical health**.
   - Example: Believing organs are decaying or infected without medical evidence.
6. **Nihilistic**:
   - Belief that **oneself, the world, or reality does not exist** or is ending.
7. **Control**:
   - Belief that one's **thoughts, feelings, or actions are being controlled** by external forces.
8. **Jealous**:
   - False belief that a partner is **unfaithful** despite lack of evidence.

Causes and Associated Conditions

1. **Psychiatric Disorders**:
   - **Schizophrenia**: Delusions are a core feature.
   - **Delusional Disorder**: Presence of one or more delusions lasting **≥1 month** without other psychotic symptoms.
   - **Bipolar Disorder**: Delusions may occur during manic or depressive episodes.
   - **Severe Depression**: May have mood-congruent delusions (e.g., guilt, worthlessness).
2. **Neurological Disorders**:
   - **Dementia**: Especially in **Lewy body dementia** and **Alzheimer's disease**.
   - **Parkinson's disease**: Delusions may arise from dopaminergic therapy.
   - **Epilepsy**: Temporal lobe epilepsy can cause delusions.
3. **Substance-Induced**:
   - **Intoxication**: Amphetamines, cocaine, cannabis, hallucinogens.
   - **Withdrawal**: Alcohol, benzodiazepines.
4. **Medical Conditions**:
   - **Infections**: CNS infections (e.g., encephalitis).
   - **Metabolic disorders**: Electrolyte imbalances, thyroid dysfunction.
   - **Brain lesions**: Tumors, strokes.

Hallucination

Definition

- **Hallucination**: Perception of sensory experiences (visual, auditory, tactile, olfactory, or gustatory) **without an external stimulus**.

Types of Hallucinations

1. **Auditory**:
    - Most common in **psychiatric disorders** (e.g., schizophrenia).
    - Perception of voices, often critical or commanding.
2. **Visual**:
    - Common in **neurological conditions** (e.g., delirium, migraines, occipital lobe lesions).
    - Seeing shapes, objects, or people that are not present.
3. **Tactile (Haptic)**:
    - Sensation of touch, often associated with substance use (e.g., formication in cocaine or alcohol withdrawal).
4. **Olfactory**:
    - Perception of odors (e.g., foul smells), often linked to **temporal lobe epilepsy** or tumors.
5. **Gustatory**:
    - Perception of unusual tastes, also associated with **temporal lobe seizures**.

Causes

1. **Psychiatric**:
    - **Schizophrenia**: Auditory hallucinations are a hallmark.
    - **Bipolar disorder**: May occur during manic or depressive episodes.
    - **Severe depression**: May include psychotic features.
2. **Neurological**:
    - **Delirium**: Visual hallucinations are common.
    - **Epilepsy**: Temporal lobe seizures may produce olfactory or gustatory hallucinations.
    - **Parkinson's disease**: Visual hallucinations are common, often due to dopaminergic therapy.
3. **Substance-Induced**:
    - **Intoxication**: Alcohol, cannabis, LSD, cocaine, amphetamines.
    - **Withdrawal**: Alcohol (e.g., delirium tremens), benzodiazepines.
4. **Medical**:
    - **Delirium** (e.g., infections, metabolic imbalances).
    - **Hypoglycemia**, **hypoxia**, or **electrolyte disturbances**.
5. **Sleep-Related**:
    - **Hypnagogic hallucinations**: Occur while falling asleep.
    - **Hypnopompic hallucinations**: Occur while waking up.
    - Common in **narcolepsy**.

Charles Bonnet Syndrome (CBS)

Definition

- CBS is characterized by **persistent or recurrent complex hallucinations** (usually visual, occasionally auditory) occurring in **clear consciousness**.
- Typically occurs against a background of **visual impairment**, though not mandatory for diagnosis.

Key Features

- Insight is usually **preserved**.
- **Complex visual hallucinations** are common in **10-30%** of individuals with severe visual impairment.
- About **1/3** find the hallucinations **unpleasant** or disturbing.
- Occurs **without significant neuropsychiatric disturbance**.

Epidemiology

- Equally distributed between **sexes**.
- No familial predisposition.
- Prevalence among visually impaired individuals: **11–15%**.

Risk Factors

1. **Advanced age**.
2. **Peripheral visual impairment**.
3. **Social isolation**.
4. **Sensory deprivation**.
5. **Early cognitive impairment**.

Associated Conditions

- Common ophthalmological conditions linked to CBS:
  - **Age-related macular degeneration**.
  - **Glaucoma**.
  - **Cataracts**.

Prognosis

- CBS is often **chronic**:
  - **88%** of individuals have CBS for **2+ years**.
  - Only **25%** experience resolution within **9 years**.
- It is **not typically transient**.

Treatment

- **Reassurance**:
  - The most effective approach, helping patients understand the benign nature of the condition.
- **Address underlying visual impairment** if possible.

> Charles Bonnet syndrome (CBS)
> - **Hallucinations (usually visual or auditory), occurring in clear consciousness.**
> - **Insight is usually preserved.**
> - **occur in 10-30 percent of individuals with severe visual impairment.**
> - **Reassurance is usually the best treatment**

Hypnogogic and hypnopompic hallucinations

Definition

- **Hypnagogic hallucinations**: Perceptual experiences that occur during the **transition from wakefulness to sleep** (**falling asleep**).
- **Hypnopompic hallucinations**: Perceptual experiences that occur during the **transition from sleep to wakefulness** (**waking up**).

Characteristics

- Can involve **visual**, **auditory**, or **tactile** sensations.
- Often vivid and can feel **realistic**.
- More common in individuals with **sleep disorders** or **psychological conditions**.

Associated Conditions

- **Narcolepsy**: Common symptom, often occurring with **cataplexy** or **sleep paralysis**.
- **Sleep deprivation** or disrupted sleep patterns.
- **Anxiety** and **stress**.
- **Substance use**: Stimulants or withdrawal from depressants.
- **Psychiatric disorders**: May overlap with hallucinations seen in schizophrenia or psychosis.

Diagnosis

- Hallucinations confined to **transitional states** of sleep.
- No other underlying psychotic disorders.
- Rule out other causes of hallucinations:
  - Neurological conditions (e.g., seizures).
  - Substance use.

Management

- **No specific treatment is required**
- **Lifestyle modifications**:
  - Maintain **consistent sleep hygiene**.
  - Reduce **stress** and address anxiety.
- **Treatment of underlying conditions**:
  - Narcolepsy: Use of **stimulants** (e.g., modafinil) and **REM-suppressing agents** (e.g., sodium oxybate).
  - Anxiety or stress: Consider **CBT** or **relaxation techniques**.
- **Avoidance of triggers**: Alcohol, recreational drugs, or excessive caffeine.

This Page Is Intentionally Left Blank

4th Edition

Notes & Notes

For MRCP
Part 1 & 2

By
Dr. Yousif Abdallah Hamad

Chapter-11

Pharmacology

Updated
2025

Basic pharmacology

Key Definitions

- **Pharmacokinetics**: The study of drug absorption, distribution, metabolism, and excretion (ADME).
- **Half-life (t½)**: Time required for plasma concentration of a drug to reduce by half.
- **Bioavailability (F)**: Fraction of an administered drug that reaches systemic circulation.
- **Volume of distribution (Vd)**: Hypothetical volume in which a drug is distributed. Vd=Dose/Plasma concentrationVd = \text{Dose} / \text{Plasma concentration}Vd=Dose/Plasma concentration.
- **Clearance (CL)**: Volume of plasma cleared of drug per unit time. CL=Rate of elimination/Plasma concentrationCL = \text{Rate of elimination} / \text{Plasma concentration}CL=Rate of elimination/Plasma concentration.
- **Steady-state concentration (Css)**: Point where drug input equals drug elimination.
- **Loading dose**: Dose required to achieve therapeutic plasma concentration quickly. Loading dose=Vd×Target concentration\text{Loading dose} = Vd \times \text{Target concentration}Loading dose=Vd×Target concentration.
- **Maintenance dose**: Dose needed to maintain steady-state. Maintenance dose=CL×Target concentration\text{Maintenance dose} = CL \times \text{Target concentration}Maintenance dose=CL×Target concentration.

Absorption

- Affected by drug solubility, ionisation, gastrointestinal pH, and first-pass metabolism.
- **First-pass metabolism** reduces bioavailability, significant in drugs like propranolol and nitroglycerin.

Distribution

- Influenced by blood flow, plasma protein binding (e.g., albumin for acidic drugs, α1-acid glycoprotein for basic drugs), and tissue binding.
- Drugs with high Vd (e.g., lipophilic drugs) distribute extensively into tissues.

Metabolism

- **Phase I reactions**:
  - Oxidation, reduction, hydrolysis (e.g., CYP450 enzymes).
  - Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase.
  - Products of phase I reactions are typically more active and potentially toxic
- **Phase II reactions**:
  - Conjugation (e.g., glucuronidation, acetylation).
  - Products are typically inactive and excreted in urine or bile.
  - Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved
  - **Conjugation reactions are affected to a lesser extent by advanced liver disease and only occur in very late stage disease**
- **First-order kinetics**: Constant proportion of drug eliminated per unit time.
- **Zero-order kinetics**: Constant amount of drug eliminated (e.g., phenytoin, ethanol).

Why is a loading dose used in amiodarone? **Because Amiodarone is widely bound in body tissues**

Drug metabolism
- phase I: oxidation, reduction, hydrolysis
- phase II: conjugation

In the elderly population, phase I reactions will usually become impaired before phase II reactions.

Renal or liver conditions lower the maintenance dose without affecting the loading dose.

The main factor influencing the time to steady-state is Half-life (t½), not dose or administration frequency.

Excretion

- **Primarily** via the kidneys. Involves filtration, reabsorption, and secretion.
- **Hepatic** elimination important for lipophilic drugs (biliary excretion).

Clinical Applications

1. **Half-life** determines dosing frequency. t½=0.693×Vd/CLt½ = 0.693 \times Vd / CLt½=0.693×Vd/CL.
2. **Drugs** with **narrow therapeutic index** (e.g., warfarin, digoxin) require monitoring.
3. **Prodrugs**: Activated by metabolism (e.g., codeine → morphine via CYP2D6).
4. **Drug interactions**:
   - Inducers (e.g., rifampicin, carbamazepine) increase metabolism.
   - Inhibitors (e.g., clarithromycin, grapefruit juice) decrease metabolism.
5. **Renal impairment** prolongs half-life of renally excreted drugs (e.g., aminoglycosides).

Most useful for drugs which have a long half-life such as:

- Amiodarone
- Digoxin
- Teicoplanin →inhibit bacterial cell wall synthesis. spectrum of activity similar to vancomycin → against Gram-positive bacteria including Staphylococci and Clostridium spp. Oral teicoplanin is effective in the treatment of pseudomembranous colitis
- Voriconazole
- Procainamide
  Fulvestrant (selective estrogen receptor degrader (SERD). used to treat hormone receptor (HR)-positive metastatic breast cancer)

Drug Absorption

Definition

- Drug absorption is the process by which a drug moves from its site of administration into the systemic circulation.

Factors Influencing Drug Absorption

1. **Route of Administration**:
   - **Oral (PO)**: Most common; affected by first-pass metabolism.
   - **Intravenous (IV)**: 100% bioavailability; bypasses absorption phase.
   - **Subcutaneous and Intramuscular (IM)**: Absorption depends on blood flow at the injection site.
   - **Sublingual (SL)**: Bypasses first-pass metabolism, providing rapid absorption (e.g., glyceryl trinitrate).
2. **Physicochemical Properties**:
   - **Solubility**: Lipophilic drugs cross membranes more easily than hydrophilic drugs.
   - **Ionisation**:
     - Non-ionised (uncharged) forms are more lipid-soluble and readily absorbed.
     - Depends on the drug's pKa and the pH of the environment (Henderson-Hasselbalch equation).
3. **Gastrointestinal (GI) Factors**:
   - **pH**: Acidic drugs (e.g., aspirin) are better absorbed in the stomach; basic drugs (e.g., propranolol) are absorbed in the intestine.
   - **Gastric Emptying**: Delayed gastric emptying slows absorption (e.g., in diabetes or with high-fat meals).
   - **Intestinal Motility**: Increased motility (e.g., diarrhoea) decreases absorption.
   - **Surface Area**: Greater surface area in the small intestine facilitates absorption.
   - **GI Enzymes**: Can degrade some drugs (e.g., insulin, degraded by digestive enzymes).
4. **First-Pass Metabolism**:
   - Drugs absorbed from the GI tract enter the liver via the portal vein and may be metabolised before reaching systemic circulation.
   - **Drugs with high first-pass metabolism should be used with caution in liver disease**, since poor hepatic function may lead to their accumulation because of increased bioavailability

Drugs with Significant First-Pass Metabolism

Drug	Impact of First-Pass Metabolism
Propranolol	Reduces bioavailability; higher oral doses required.
Nitroglycerin	Extensive first-pass metabolism; ineffective orally, used sublingually.
Verapamil	Reduces bioavailability; higher oral doses needed for efficacy.
Morphine	Undergoes hepatic metabolism; variable oral bioavailability.
Lidocaine	Poor oral bioavailability; used IV or topically.
Salbutamol	High first-pass metabolism reduces systemic bioavailability.
Estradiol	Extensive first-pass metabolism; requires transdermal or other routes.
Imipramine	Variable bioavailability; affected by first-pass metabolism.
Levodopa	Converted to dopamine peripherally; co-administered with carbidopa to reduce first-pass metabolism effects.

What is the reason for a different dose of sublingual glyceryl trinitrate (GTN) and oral isosorbide mononitrate?
⇨ **First-pass metabolism**

5. **Formulation of the Drug**:
    - **Immediate-Release vs. Controlled-Release**: Formulation affects the rate and extent of absorption.
    - Particle size, excipients, and coating can alter dissolution and absorption rates.
6. **Blood Flow to the Absorption Site**:
    - Increased blood flow (e.g., after exercise) enhances absorption (e.g., from IM or SC sites).
7. **Drug-Drug and Drug-Food Interactions**:
    - **Food**: Can enhance (e.g., griseofulvin) or reduce (e.g., tetracyclines with calcium) absorption.
    - **Drugs**: Antacids reduce absorption of drugs like ciprofloxacin by chelation.

Bioavailability (F)

- The fraction of an administered drug that reaches systemic circulation.
- Influenced by first-pass metabolism and absorption efficiency.
- **The bioavailability of an intravenously administered drug is 100% and does not change in renal failure**.

Clinical Examples

- **Pro-drugs** (e.g., enalapril): Require absorption and metabolic activation.
- **Drugs affected by pH**:
    - Proton pump inhibitors (e.g., omeprazole) reduce absorption of acidic drugs.
    - Alkalinising agents enhance excretion of acidic drugs (not absorption but relevant to pharmacokinetics).
- **Subcutaneous Absorption**:
    - Insulin absorption varies with site (abdomen > arm > thigh).

Key Points for MRCP

1. Drugs with significant first-pass metabolism (e.g., propranolol, verapamil) require dose adjustments in liver impairment.
2. Absorption rates differ with drug formulations; sustained-release drugs have slower but prolonged absorption.
3. Lipophilic drugs are better absorbed orally than hydrophilic drugs.
4. Food interactions are important; for example, avoid calcium-containing foods with tetracyclines.
5. First-pass metabolism affects bioavailability; sublingual or parenteral routes bypass this issue.

Lipid soluble drug vs lipid insoluble drug

lipid soluble drug	lipid insoluble drug
have good gastrointestinal absorption	**have poor gastrointestinal absorption**
can be given orally	**may need to be given parenterally**
will be widely distributed in the body (large volume of distribution)	has limited distribution (may not cross blood-brain barrier or placenta and less likely to be stored in fat tissue)
usually requires metabolism before elimination (to decrease lipid solubility)	**may be eliminated without metabolism**
often have a long plasma half-life (prolonged by 'reservoir' of drug in tissues and by requirement for metabolism).	often have a short plasma half-life as elimination does not require metabolism.

MRCPUK-part-1-Sep 2017: **What is the mechanism that make salmeterol acts as a LABA?**
→ **Its long duration results from its high lipid solubility**

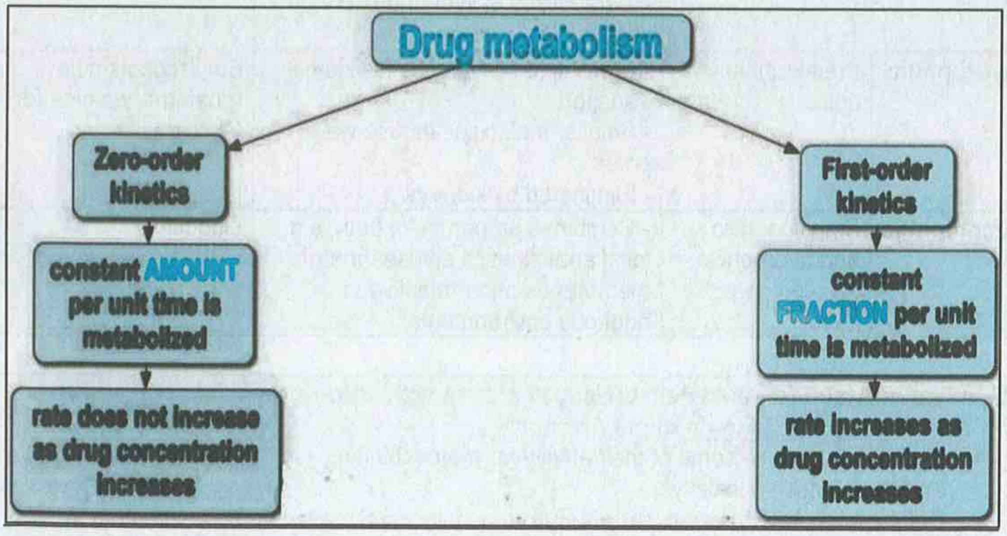
Lipophilic, Hydrophilic and Amphiphilic

Type	Chemical Nature	Clinical Significance	Example
Lipophilic	Predominantly nonpolar	- Diffuse across lipid bilayers easily - Administered topically - Cross blood-brain barrier - Metabolised in liver and excreted via bile	Scopolamine (tertiary amine for motion sickness)
Hydrophilic	Predominantly polar	- Cross lipid bilayers via facilitated transport - Smaller molecules diffuse via pores - Eliminated by kidneys	Butylscopolamine (quaternary amine for GI colic)
Amphiphilic	Both lipophilic and hydrophilic	- Combines properties of both; e.g., local anaesthetics diffuse through membranes and are active in aqueous environments	Lidocaine

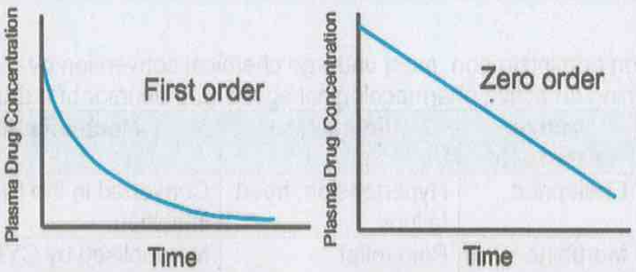
What is the reason for phenytoin toxicity in patient with chronic renal failure?
→ **Decreased protein binding of phenytoin**
- In CKD, drugs lose some of their affinity for protein binding →↑↑ availability of free drug at any given dose → toxicity
- Because laboratory assays for **phenytoin** usually measure total drug concentration, this give a false re-assurance (**drug level may be within therapeutic range**)
- In CKD dose reduction of phenytoin is therefore required
- Other drugs may cause same problem → **sodium valporate** and **warfarin**

First-Order Kinetics vs Zero-Order Kinetics

Feature	First-Order Kinetics	Zero-Order Kinetics
Definition	A constant **proportion** of drug is eliminated per unit time.	A constant **amount** of drug is eliminated per unit time.
Rate of Elimination	Proportional to drug concentration.	Independent of drug concentration (pathway saturated).
Plasma Concentration-Time Curve	Exponential decline.	Linear decline.
Half-Life (t½)	Constant; does not depend on drug concentration.	Varies with drug concentration; not constant.
Enzyme Saturation	Enzymes are **not saturated** under normal conditions.	Enzymes are **saturated** at therapeutic/toxic concentrations.
Examples	Most drugs (e.g., paracetamol, penicillin).	Phenytoin (high doses), ethanol, aspirin (high doses).
Steady-State	Achieved after 5 half-lives.	Difficult to predict steady-state due to non-linear elimination.
Clinical Relevance	Dose adjustments are proportional to drug levels.	Small dose increases can lead to disproportionately higher plasma concentrations, increasing toxicity risk.



FIRST ORDER & ZERO ORDER KINETICS



First order

- Constant fraction of drug eliminated per unit time
- Rate of drug elimination proportional to drug plasma concentration

Zero order

- Constant amount of drug eliminated per unit time
- Rate of drug elimination independent of drug plasma concentration

Key MRCP Exam Points

1. **First-order kinetics** is more common in clinical practice and applies to most drugs under therapeutic doses.
2. **Zero-order kinetics** occurs with enzyme saturation, making dose adjustments critical to avoid toxicity.
3. Drugs with **zero-order kinetics** (e.g., phenytoin) require careful monitoring and titration due to their non-linear elimination.

Drugs exhibiting zero-order kinetics

- **Phenytoin**
- **Salicylates (e.g. high-dose aspirin)**
- **Heparin**
- **Ethanol**

Prodrugs

Definition

- A drug that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent; (a precursor of a drug).

Prodrug	Active Metabolite	Clinical Use	Mechanism/Significance
Enalapril	Enalaprilat	Hypertension, heart failure	Converted in the liver for ACE inhibition.
Codeine	Morphine	Pain relief	Metabolised by CYP2D6 for opioid receptor activation.
Clopidogrel	Active thiol metabolite	Antiplatelet (e.g., ACS, PCI)	Requires CYP2C19 activation for P2Y12 receptor inhibition.
Levodopa	Dopamine	Parkinson's disease	Crosses BBB and converted to dopamine; co-administered with carbidopa to prevent peripheral metabolism.
Simvastatin	Active hydroxy acid	Hyperlipidaemia	Hydrolysed in the liver to inhibit HMG-CoA reductase.
Tamoxifen	Endoxifen	Breast cancer (ER+ve)	Converted by CYP2D6 for estrogen receptor antagonism.
Aspirin	Salicylic acid	Antiplatelet, analgesic, anti-inflammatory	Hydrolysed in plasma and liver for COX inhibition.
Valaciclovir	Acyclovir	Herpes simplex and zoster infections	Better oral bioavailability than acyclovir.
Prednisone	Prednisolone	Inflammatory and autoimmune diseases	Activated in the liver for corticosteroid effects.
5-Fluorouracil (Capecitabine)	Fluorouracil	Cancer (e.g., colorectal)	Capecitabine is converted to fluorouracil in tumour tissues for selective cytotoxicity.

Key Points for MRCP

1. Prodrugs require **metabolic activation** to exert their pharmacological effect.
2. Activation often occurs in the liver but can be site-specific (e.g., tumour cells for capecitabine).
3. Genetic polymorphisms (e.g., CYP2D6, CYP2C19) can affect prodrug metabolism and efficacy (e.g., clopidogrel, tamoxifen).
4. Prodrugs improve pharmacokinetic properties such as bioavailability (e.g., valaciclovir) or reduce systemic side effects.

Clinical trial: phases

Clinical trials are commonly classified into 4 phases;

Phase	Goal	Notes
I	Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies	Conducted on healthy volunteers
II	Assess efficacy + dosage	Involves small number of patients affected by particular disease May be subdivided into: • IIa - assesses optimal dosing • **IIb - assesses efficacy**
III	Assess effectiveness	Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments
IV	Postmarketing surveillance	Monitors for long-term effectiveness and side-effects

P450 Enzyme System

Feature	Details
Definition	A group of enzymes (cytochrome P450, CYP450) responsible for drug metabolism.
Location	Primarily in the **liver**; also in the intestines, kidneys, and lungs.
Function	Catalyses oxidation (Phase I metabolism) of lipophilic drugs to make them more water-soluble for elimination.
Subtypes	Major subtypes: CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2, CYP2E1.

Key Enzyme Subtypes and Their Substrates

Subtype	Key Substrates
CYP3A4	Statins, calcium channel blockers, macrolides, benzodiazepines.
CYP2D6	Codeine (to morphine), metoprolol, tamoxifen.
CYP2C9	Warfarin, phenytoin, NSAIDs.
CYP2C19	Clopidogrel, proton pump inhibitors, diazepam.
CYP1A2	Theophylline, caffeine.
CYP2E1	Paracetamol (to toxic metabolites), ethanol.

CYP450 Inducers and Inhibitors

Inducers (Increase enzyme activity):

Inducers of the P450 system include:	
• antiepileptics: phenytoin, carbamazepine • barbiturates: phenobarbitone • rifampicin • St John's Wort	• chronic alcohol intake • griseofulvin • smoking (affects CYP1A2, reason why smokers require more aminophylline)
Effect: Reduces plasma levels of substrates, lowering drug efficacy.	

Inhibitors (Decrease enzyme activity):

Inhibitors of the P450 system include	
• antibiotics: ciprofloxacin, erythromycin • isoniazid • cimetidine, omeprazole • amiodarone • allopurinol • imidazoles: ketoconazole, fluconazole	• SSRIs: fluoxetine, sertraline • sulphonamides • Disulfiram • ritonavir • **sodium valproate** • acute alcohol intake • quinupristin
Effect: Increases plasma levels of substrates, increasing toxicity risk.	

Isoniazid inhibits the P450 system

3 "O" antibiotics inhibitOrs → isOniazid , ciprOfloxacine , erythrOmycin
1 "C " antibiotic induCer → rifampiCine

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto- induction

Clinical Relevance for MRCP

1. **Drug-Drug Interactions**:
   - Inducers: Reduce efficacy of warfarin, oral contraceptives, statins.
   - Inhibitors: Increase toxicity of warfarin, phenytoin, and statins.
2. **Pharmacogenomics**:
   - Genetic polymorphisms (e.g., CYP2D6) affect drug metabolism (e.g., codeine → morphine conversion).
3. **Toxic Metabolism**:
   - CYP2E1: Converts paracetamol into toxic NAPQI at high doses.
4. **First-Pass Metabolism**:
   - Many CYP450 enzymes are involved in extensive first-pass metabolism (e.g., propranolol, verapamil).

P450 drug interactions: more detail

the most important and common reason for drug interactions is the P450 **CYP3A4 system**. The table below shows the main enzyme systems that are affected by common drugs.

P450 system	Substrates	Inhibitors	Inducers
CYP3A4	Macrolides Antiretrovirals Calcium channel blockers simvastatin	Macrolides Protease inhibitors (including ritonavir) Imidazoles grapefruit juice	Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's Wort
CYP2D6	Tricyclic antidepressants Antipsychotics	SSRIs Ritonavir	
CYP2C9	Warfarin Sulfonylureas	Imidazoles Amiodarone Sodium valproate	Rifampicin
CYP1A2	Theophylline	**Ciprofloxacin**	Smoking Omeprazole
CYP2E1	Alcohol		Chronic alcohol Isoniazid

CYP-2C8	CYP-2C18/19	CYP-2D6
Omeprazole	Diazepam	Tricyclic antidepressants
Diazepam	Tricyclic antidepressants	β-blockers
Barbiturates	Omeprazole	Dihydrocodeine
	Proguanil	Ecstasy (MDMA)
		Selective serotonin reuptake inhibitors

Therapeutic Drug Monitoring (TDM)

Definition

- Therapeutic drug monitoring (TDM) involves measuring drug concentrations in plasma or blood to optimise therapy, ensure efficacy, and minimise toxicity.

Indications for TDM

1. **Narrow Therapeutic Index**:
   - Drugs with a small margin between therapeutic and toxic levels (e.g., digoxin, lithium).
2. **Unpredictable Pharmacokinetics**:
   - Drugs affected by factors like age, renal/hepatic function, or genetic variability (e.g., phenytoin).
3. **Potential for Severe Toxicity**:
   - Monitoring helps prevent adverse effects in drugs with high toxicity risks (e.g., aminoglycosides).
4. **Monitoring Compliance**:
   - Used in chronic conditions to confirm adherence (e.g., antiepileptics).
5. **Drug Interactions**:
   - Drugs that interact via metabolism or excretion require monitoring to adjust dosing (e.g., warfarin).

Drugs Commonly Monitored

Drug Class	Examples	Target Range
Antiepileptics	Phenytoin, carbamazepine, valproate	Phenytoin: 10–20 µg/mL
Antibiotics	Vancomycin, gentamicin	Vancomycin: 10–20 mg/L (trough level)
Anticoagulants	Warfarin	INR: 2.0–3.0 (most indications)
Immunosuppressants	Ciclosporin, tacrolimus	Tacrolimus: 5–15 ng/mL
Cardiac Drugs	Digoxin	0.5–2.0 ng/mL
Psychotropics	Lithium	0.6–1.2 mmol/L (maintenance)
Bronchodilators	Theophylline	5–15 µg/mL

Sample Timing:

- Critical for interpretation:
  - **Trough Level**: Taken immediately before next dose (e.g., vancomycin).
  - **Peak Level**: Taken shortly after drug administration (e.g., aminoglycosides).

Drug induced manifestations

Drug causes gingival hyperplasia

Gingival hyperplasia: phenytoin, ciclosporin, calcium channel blockers and AML

Drug causes of gingival hyperplasia

- phenytoin
- Ciclosporin
- **calcium channel blockers** (especially nifedipine)

Other causes of gingival hyperplasia include

- acute myeloid leukaemia (myelomonocytic and monocytic types)

Drugs causing photosensitivity

- thiazides
- tetracyclines, sulphonamides, ciprofloxacin
- amiodarone
- NSAIDs e.g. piroxicam
- psoralens
- sulphonylureas

Drugs causing specific skin reactions

- **Psoriatic-type reactions are most commonly caused by beta-blockers**
- Antibiotics may cause lupus-type reactions, erythema multiforme, Stevens–Johnson syndrome and erythroderma
- Warfarin is associated with alopecia, as are cytotoxic agents and antithyroid agents
- Phenytoin may cause both acne and gingival hyperplasia

Drug affects folic acid metabolism

Drugs which inhibit dihydrofolate reductase are:

- Methotrexate
- **Pyrimethamine**, and
- Trimethoprim.

Drugs which interfere with absorption/storage of folate are:

- Phenytoin
- Primidone, and
- Oral contraceptives.

Drug causes SIADH

most commonly causes SIADH	Other causes
• Thiazide diuretics • Vincristine • Vinblastine • Cyclophosphamide	• Chlorpropamide • Carbamazepine • Phenothiazines • Tricyclic antidepressants • Clofibrate • Oxytocin • Vasopressin • Morphine • Barbiturates • Nicotine

Drug causes of urticaria

The following drugs commonly cause urticaria:

- **aspirin**
- penicillins
- NSAIDs
- opiates

Drugs induced galactorrhoea

Drug causes of raised prolactin

- **metoclopramide**, Domperidone
  - ⇨ **Domperidone is a dopamine antagonist producing large rises in prolactin concentrations.**
- phenothiazines
- haloperidol
- Cimetidine produces hyperprolactinaemia **only** when given intravenously (IV).
- very rare: SSRIs, opioids

Drugs associated with gynaecomastia

- **Spironolactone (the** most common**),** causes gynaecomastia by several **mechanisms.**
  - ⇨ **block androgen production** by inhibiting enzymes in the testosterone synthetic pathway,
  - ⇨ **block receptor binding of testosterone** and dihydrotestosterone.
  - ⇨ **increases free oestrogen levels** by displace oestradiol from sex hormone binding globulin (SHBG)

Other causes

• inhibitors of testosterone synthesis: ⇨ ketoconazole ⇨ metronidazole ⇨ cimetidine, Omeprazole ⇨ etomidate, and ⇨ cisplatin. • Oestrogens: ⇨ **Digoxin** → direct action at oestrogen receptors. • LHRH analogues • Finasteride.	• marijuana • heroin • isoniazid • Ciclosporin • calcium-channel blockers • **ACE inhibitors** • tricyclic antidepressants • busulphan • diazepam

Drug-induced impaired glucose tolerance

- **Drugs which are known to cause impaired glucose tolerance include:**
  - ⇨ thiazides, furosemide (less common)
  - ⇨ steroids
  - ⇨ tacrolimus, ciclosporin
  - ⇨ interferon-alpha
  - ⇨ nicotinic acid
  - ⇨ atypical antipsychotics e.g. olanzapine
- **Beta-blockers an glycemic status:**
  - ⇨ beta -2-adrenergic antagonism → inhibition of hepatic gluconeogenesis
    - **unselective beta-blockade associated with hypoglycemia** (e.g. **propranolol** rather than the use of beta-1 selective blockers e.g. atenolol, metoprolol).
    - **selective beta-1 blockers** would not lead to hypoglycaemia - however "...in patients with abnormal energy requirements or metabolism, administration of beta 1-selective-adrenergic antagonists may be associated with hypoglycaemia
  - ⇨ Beta-blockers cause a slight impairment of glucose tolerance.
  - ⇨ They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

Drug-induced lupus erythematosus

The most commonly associated drugs

- procainamide
- hydralazine 2,
- anti-TNF alpha agents,
- statins
- isoniazid
- **minocycline**.

Drug-induced Pancytopaenia

Trimethoprim may cause pantcytopaenia

Drug causes of Pancytopaenia

- cytotoxics
- antibiotics: trimethoprim, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole (causes both agranulocytosis and pancytopaenia)
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide
- Although both **azathioprine** and **mesalazine** cause pancytopenia, it is **more commonly seen in patients undergoing azathioprine therapy**.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (probable immune mediated)

- quinine
- abciximab
- NSAIDS
- diuretics: furosemide
- antibiotics: penicillins, sulphonamides, rifampicin
- anticonvulsants: carbamazepine, valproate
- heparin

Drug-induced long QT

Commonly medications that cause QT prolongation		
class	**Examples**	
Antiarrhythmic	• Amiodarone • Disopyramide • Ibutilide	• Procainamide • Quinidine • Sotalol
antipsychotics	• Chlorpromazine • Clozapine • Haloperidol	• Quetiapine • Risperidone • Thioridazine
antibiotics	• Azithromycin • Clarithromycin • Erythromycin • Ciprofloxacin • Levofloxacin	• Ofloxacin • Trimethoprim – sulpha • Ketoconazole • Fluconazole • itraconazole
Antidepressants	• Amitriptyline • Citalopram • Desipramine • Doxepin • fluoxetine	• Imipramine • Nortriptyline • Paroxetine • Sertraline • venlavaxine
Antiemetics	• Ondansetron	• prochlorperazine

Drugs causing ocular problems

Visual disturbance	cataract	Corneal opacities	Optic neuritis	Retinopathy	Blue tinge in vision	Yellow-green tinge
Drug	steroids	Amiodarone Indomethacin	Ethambutol Amiodarone Metronidazole	Chloroquine, quinine	**Sildenafil**	**Digoxin**

Visual changes secondary to drugs

- blue vision: Viagra ('the blue pill')
- yellow-green vision: digoxin

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

Drug induced photosensitivity

Rash on the forearms and face is typical of a photosensitivity rash

- Thiazides
- Tetracyclines, sulphonamides, ciprofloxacin
- Amiodarone
- NSAIDs e.g. Piroxicam
- Psoralens
- Sulphonylureas

Mnemonic: **FAST-N** (**F**luoroquinolones eg: cipro. **A**miodarone. **S**ulfo.**T**etracyclines. **N**SAIDs)

Drug induced ototoxicity

- **Causes**
  - ⇨ Aminoglycosides
    - ▪ Streptomycin → irreversible cochlear and vestibular dysfunction
  - ⇨ Platinum-based antineoplastic agents,
  - ⇨ Salicylates
  - ⇨ Quinine
  - ⇨ Loop diuretics.
- Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus.
- The time of onset is unpredictable:
  - ⇨ marked hearing loss can occur even after a single dose.
  - ⇨ may occur several weeks or months after completion of antibiotic or antineoplastic therapy.
- Usually irreversible with most agents.

Drug induced seizures

- Drugs that cause seizures as a drug reaction include:
  - ⇨ Isoniazid (vitamin B6 deficiency)
  - ⇨ Bupropion,
  - ⇨ Imipenem/cilastatin
  - ⇨ Tramadol
  - ⇨ Enflurane

Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane.

With seizures, I BITE my tongue.

Drug causes erythema multiforme, and the Stevens-Johnson syndrome subtype.

- **Allopurinol → (the Most commonly associated)**
- Recent drugs - nevirapine, lamotrigine, sertraline, pantoprazole, tramadol
- Antibiotics - sulphonamides, co-trimoxazole, penicillin, cephalosporins, fluoroquinolones, vancomycin
- NSAIDs - piroxicam, fenbufen, ibuprofen, ketoprofen, naproxen, tenoxicam, diclofenac, sulindac
- Anti-TB - rifampicin, ethambutol, isoniazid, pyrazinamide
- Anticonvulsants - barbiturates, carbamazepine, phenytoin, valproate, lamotrigine
- Antifungals - fluconazole, nystatin, griseofulvin
- Antidepressants - lamotrigine, sertraline.
- **Sulfasalazine**

Drug-induced ethanol intolerance (disulfiram-like reaction)

- As in the case with disulfiram, the underlying mechanism is believed to be the accumulation of acetaldehyde in the blood, due to inhibition of the hepatic aldehyde dehydrogenases.
- drugs which can produce DISULFIRAM like reaction when taken with Alcohol:
  - ⇨ chloramphenicol,
  - ⇨ furazolidone,
  - ⇨ **nitroimidazole antibiotics, including metronidazole**, and
  - ⇨ quinacrine,
  - ⇨ First-generation sulfonylureas, e.g. tolbutamide and chlorpropamide
  - ⇨ cephalosporins, including cefoperazone, cefamandole and cefotetan
  - ⇨ antifungal eg: Griseofulvin
  - ⇨ Procarbazine

Disulfiram-Like Reaction

- **Definition**: A reaction that mimics the effects of disulfiram (used in alcohol dependence), causing severe **flushing, nausea, vomiting, hypotension, and tachycardia** upon alcohol ingestion.

Mechanism:

- Inhibition of **aldehyde dehydrogenase** → Accumulation of **acetaldehyde** after alcohol consumption.

Common Drugs Causing It:

1. **Antibiotics**: Metronidazole, cefoperazone, cefotetan.
2. **Antifungals**: Griseofulvin.
3. **Other**: Sulfonylureas (e.g., chlorpropamide), procarbazine.

Clinical Importance:

- Advise **alcohol avoidance** during and after treatment with these drugs to prevent symptoms.

Disulfiram → inhibitor of Aldehyde dehydrogenase, which is located in the mitochondria
Fomepizole → inhibitor of Alcohol dehydrogenase, which is located in the cytosol

The target of disulfiram is located in which cellular compartments?
⇨ Mitochondria

Drugs Acting on Serotonin (5-HT) Receptors

Class	Examples	Receptor Target	Clinical Use
5-HT1 Agonists	- Sumatriptan, rizatriptan	5-HT1B/1D	Migraine (vasoconstriction of cranial vessels).
5-HT2 Antagonists	- Risperidone, olanzapine	5-HT2A/2C	Schizophrenia, bipolar disorder (antipsychotics).
5-HT3 Antagonists	- Ondansetron, granisetron	5-HT3	Nausea and vomiting (e.g., chemotherapy-induced).
5-HT4 Agonists	- Prucalopride	5-HT4	Chronic constipation (stimulates gut motility).
SSRIs (Selective Serotonin Reuptake Inhibitors)	- Fluoxetine, sertraline	Presynaptic serotonin reuptake inhibition	Depression, anxiety disorders.
SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)	- Venlafaxine, duloxetine	Presynaptic serotonin reuptake inhibition	Depression, anxiety, neuropathic pain.
MAOIs (Monoamine Oxidase Inhibitors)	- Phenelzine, tranylcypromine	Prevent serotonin breakdown	Depression (rarely used due to interactions).
Atypical Antidepressants	- Mirtazapine	5-HT2/5-HT3 antagonist	Depression (enhances sleep, appetite).

Class	Examples	Receptor Target	Clinical Use
Serotonin Agonist-Antagonists	- Trazodone	5-HT2 antagonist, weak reuptake inhibition	Depression, insomnia.
Ergot Alkaloids	- Ergotamine	5-HT1 and others	Migraine, cluster headaches.
LSD (Lysergic Acid Diethylamide)	- Recreational drug	Multiple 5-HT receptors	Hallucinogenic effects (not therapeutic).

Key Points for MRCP

1. Serotonin receptors are involved in diverse systems: CNS, GI tract, and vascular regulation.
2. Drugs targeting **5-HT1 receptors** are key in migraine treatment.
3. **5-HT3 antagonists** are essential in managing chemotherapy-induced nausea.
4. **SSRIs and SNRIs** are first-line treatments for depression and anxiety.
5. Be aware of **serotonin syndrome** risk with drugs affecting serotonin pathways (e.g., SSRIs, MAOIs, triptans).

Drugs that can be cleared with Hemodialysis - mnemonic: **BLAST**

• **B**arbiturate • **L**ithium • **A**lcohol (inc methanol, ethylene glycol) • **S**alicylates • **T**heophyllines (charcoal hemoperfusion is preferable)	**Drugs which cannot be cleared with HD include** • Tricyclics • Benzodiazepines (diazepam, midazolam, alprazolam) • Dextropropoxyphene (co-proxamol) • Digoxin, β-blockers

Antimicrobial

Antibiotics: General overlook

Antibiotics: bactericidal vs. bacteriostatic

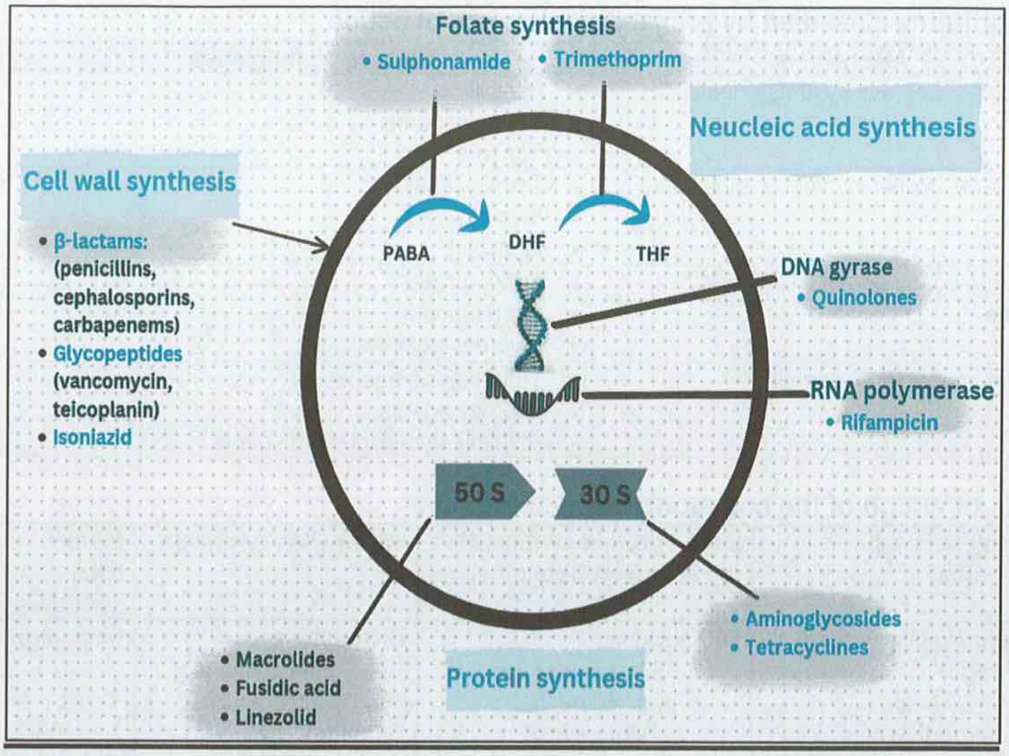
Bactericidal antibiotics (kill the bacteria)	Bacteriostatic (suppress the growth of bacteria)
• Penicillins • Cephalosporins • Aminoglycosides • Nitrofurantoin • Metronidazole • Quinolones • Rifampicin • Isoniazid	• Chloramphenicol • Macrolides • Tetracyclines • Sulphonamides • Trimethoprim

Antibiotics classified by primary mechanism of action

Mechanism	Classes of antibiotics
Bacterial cell wall synthesis inhibitors	• Penicillins • Cephalosporins • Penems
Bacterial protein synthesis inhibitors	• Tetracyclines • Macrolides • Linezolid
Agents acting against DNA and/or folate	• Sulfonamides • Trimethoprim • Fluoroquinolones
Antimycobacterial agents	• Tuberculosis agents • Leprosy agents • Atypical mycobacterium agents

Site of action of the commonly used antibiotics

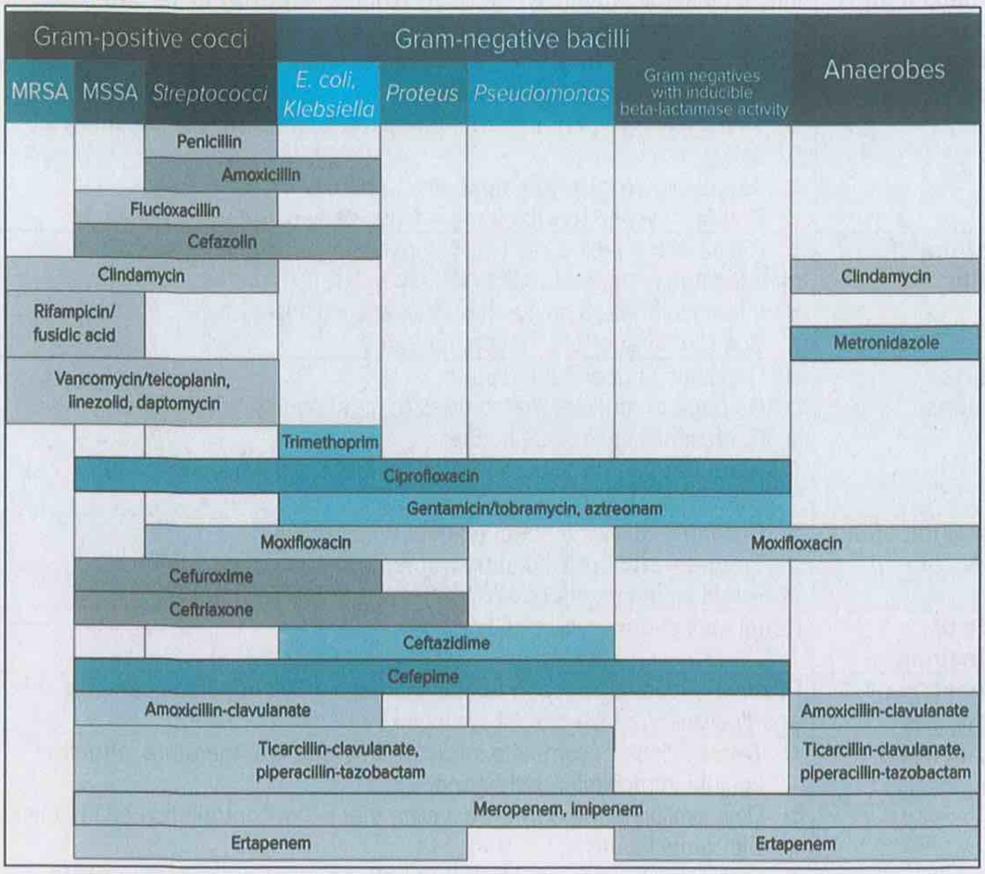
Inhibit cell wall formation	Inhibit protein synthesis (by acting on ribosome)	Inhibit DNA synthesis	Inhibit RNA synthesis
Peptidoglycan cross-linking • β-lactams (penicillins, cephalosporins, carbapenems) **↓Peptidoglycan synthesis** • Glycopeptides (vancomycin, teicoplanin) • isoniazid (Those organisms lacking a cell wall are resistant to these drugs e.g. Chlamydia's)	**50S subunit** • chloramphenicol • macrolides (e.g. erythromycin) • fusidic acid • (Quin/Dalfo)pristin • Linezolid **30S subunit** • aminoglycosides (cause misreading of mRNA) • tetracyclines	**DNA gyrase** • quinolones (e.g. ciprofloxacin) **Damages DNA** • metronidazole **Inhibits folic acid formation** • sulphonamides • trimethoprim	Rifampicin



Antibiotics: anaerobic activity

antibiotics have anti-anaerobic activity	antibiotics do not have anti-anaerobic activity
• penicillins • cephalosporins (except ceftazidime) • erythromycin • metronidazole • tetracycline	• gentamicin • ciprofloxacin • ceftazidime

Microbial coverage of antibiotics for gram-positive cocci, gram-negative bacilli, and anaerobes.



Tetracyclines

Mechanism of action	Inhibit bacterial protein synthesis by binding reversibly to the **30S** ribosomal subunit (bacteriostatic effect)
Agents and usual doses	➲ Minocycline (oral or IV): 200 mg once, followed by 100 mg every 12 hours (maximum: 400 mg daily). ➲ Tetracycline (oral or IV): 250 to 500 mg 4 times daily or 500 mg twice daily. ➲ doxycycline (oral): 100 mg every 12 hours ➲ Demeclocycline (oral): 50 mg 4 times daily or 300 mg twice daily.
Spectrum of activity	➲ Bacteria that lack a cell wall (e.g, Mycoplasma pneumoniae) ➲ Community-acquired MRSA (doxycycline) ➲ Intracellular bacteria, such as Rickettsia, Chlamydia. ➲ Borrelia burgdorferi, Vibrio cholerae
Adverse reactions	➲ Deposition in bones and teeth ➲ Damage to mucous membranes (e.g., esophagitis, GI upset) ➲ Photosensitivity (sunburn-like) ➲ Rare: Pseudotumor cerebri (Benign intracranial hypertension) → headaches, visual disturbances
Contraindications	➲ Children < 8 years of age (except doxycycline) ➲ Pregnant and breastfeeding women ➲ Renal failure (except doxycycline)
Route of elimination	Renal except doxycycline (GI)
Mechanism of resistance	Plasmid-encoded transport pumps increase efflux out of the bacterial cell and decrease uptake of tetracyclines.
Special notes	➲ Tetracyclines accumulate intracellularly and are, therefore, effective against intracellular pathogens ➲ Doxycycline is the only tetracycline that is not contraindicated in patients with renal failure ➲ Milk (Ca^{2+}), antacids (Mg^{2+}), or Fe^{2+} (iron supplements) →inhibit intestinal absorption of tetracyclines. ➲ Demeclocycline May be used as a diuretic for SIADH because it is an ADH antagonist.

Macrolides

Mechanism of action	Inhibit bacterial protein synthesis by binding to 23S ribosomal RNA molecule of the **50S subunit** (bacteriostatic effect)
Agents and usual doses	➲ Clarithromycin (oral or IV): 500 mg every 12 hours ➲ Azithromycin (oral or IV): 500 mg once daily ➲ Erythromycin (oral or IV): 250 to 500 mg every 6 to 12 hours; maximum: 4 g daily.
Spectrum of activity	➲ Atypical pneumonia caused by: Mycoplasma pneumonia, Legionella, Chlamydophila pneumoniae ➲ Gram-positive cocci ➲ Neisseria spp (2nd line prophylaxis for N. meningitidis), N. gonorrhoeae ➲ Bordetella pertussis ➲ STIs caused by Chlamydia ➲ Mycobacterium avium ➲ H. pylori (clarithromycin is the part of triple therapy)
Adverse reactions	➲ Increased intestinal motility → GI upset ➲ QT-interval prolongation , arrhythmia ➲ Acute cholestatic hepatitis ➲ Eosinophilia, Rash
Contraindications	➲ Pregnancy (except Azithromycin which is commonly used in pregnancy) ➲ Hepatic failure (except erythromycin which can be used caustically)
Route of elimination	Biliary
Mechanism of resistance	Methylation of the binding site of 23S rRNA prevents the macrolide from binding to rRNA.
Special notes	➲ Erythromycin used for the treatment of gastroparesis because it increases GI motility. ➲ Erythromycin →↑ effect of warfarin. ➲ Erythromycin and clarithromycin →↑ theophylline serum concentrations ➲ Erythromycin and clarithromycin → CYP3A4 inhibition (cytochrome P450 inhibitors) ➲ **bacteriostatic at low doses and bactericidal at high doses**

Erythromycin is used in gastroparesis as it has prokinetic properties, Promotes gastric emptying

Fluoroquinolones

Mechanism of action	Inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV → inhibition of DNA replication and transcription (bactericidal effect)
Agents	➲ 1st generation: Nalidixic acid (oral) ➲ 2nd generation: Norfloxacin, Ciprofloxacin, Ofloxacin (oral) ➲ 3rd generation: levofloxacin (oral or IV): ➲ 4th generation: Moxifloxacin, Gemifloxacin ➲ Respiratory fluoroquinolones: Levofloxacin, Moxifloxacin, and Gemifloxacin
Spectrum of activity	➲ Levofloxacin, moxifloxacin, and gemifloxacin (respiratory quinolones): ▪ Atypical bacteria (e.g., Legionella spp., Mycoplasma spp., Chlamydophila pneumoniae) and anaerobes. ▪ Gemifloxacin is highly potent against penicillin-resistant pneumococci. ▪ Moxifloxacin: 2nd-line treatment of TB if 1st line not tolerated and in multidrug resistant tuberculosis. ➲ Norfloxacin, ciprofloxacin, and ofloxacin ▪ Gram-negative rods causing UTI and GI infections and Some gram-positive pathogens ▪ Genitourinary infections caused by Neisseria gonorrhoeae, Chlamydia trachomatis ▪ Ciprofloxacin primarily targets gram-negative bacilli, including Pseudomonas aeruginosa.
Adverse reactions	➲ Lower the seizure threshold (↑ risk in patients taking NSAIDs and those with epilepsy) ➲ Peripheral neuropathy ➲ QT prolongation ➲ Exacerbation of myasthenia gravis ➲ Tendon rupture, especially of the Achilles tendon
Contraindications	➲ Pregnancy, breastfeeding and children. ➲ Epilepsy, stroke, CNS lesions/inflammation ➲ QT prolongation ➲ Myasthenia gravis
Route of elimination	➲ Primarily renal (via glomerular filtration and tubular secretion) ➲ Moxifloxacin undergoes biliary excretion.
Mechanism of resistance	➲ Chromosome-encoded mutation in DNA gyrase and topoisomerase IV enzymes ➲ Altered cell wall permeability ➲ Plasmid-encoded mutations in efflux pump proteins
Special notes	➲ Ciprofloxacin inhibits cytochrome P450 →↑risk for drug interactions ➲ Milk (Ca^{2+}), antacids (Mg^{2+}), or Fe^{2+} (iron supplements) →inhibit intestinal absorption of fluoroquinolone. ➲ Coadministration of other medications that prolong the QT interval should be avoided.

Aminoglycosides

Mechanism of action	Inhibit bacterial protein synthesis by binding to **30S subunit** of the bacterial ribosome (bactericidal effect)
Agents	➲ IV or IM gentamicin: 5 mg/kg once daily or divided ➲ IV or IM amikacin: 15 mg/kg once daily or divided (max. per dose 1.5 g once daily) IV or IM tobramycin: 3 mg/kg daily in 3 divided doses ➲ IV or IM streptomycin ➲ Oral neomycin ➲ Kanamycin
Spectrum of activity	➲ Gram-negative rod infections ➲ Amikacin, gentamicin, and tobramycin are also active against **Pseudomonas** ➲ Not effective against anaerobes (aminoglycosides require oxygen to be absorbed by cells) ➲ Neomycin, which is not absorbed systemically, is administered orally to prepare the gut for bowel surgery. ➲ Streptomycin is used as a second-line treatment for Mycobacterium tuberculosis and M. avium-intracellulare
Adverse reactions	➲ Nephrotoxicity ➲ Ototoxicity and vestibulotoxicity (risk of ototoxicity is higher when used concurrently with loop diuretics) → Tinnitus, Ataxia, Vertigo ➲ Neuromuscular blockade ➲ Teratogenicity
Contraindications	➲ Myasthenia gravis ➲ Botulism ➲ Pregnancy
Route of elimination	Renal (via glomerular filtration)
Mechanism of resistance	Inactivation via acetylation, phosphorylation, and/or adenylation by secreted bacterial transferase enzymes
Special notes	➲ Aminoglycosides should not be combined with other nephrotoxic drugs (e.g., NSAIDS, vancomycin, furosemide). ➲ Gentamicin is more potent than tobramycin against Serratia spp, while tobramycin is more potent than gentamicin against Pseudomonas aeruginosa. ➲ Once daily administration of aminoglycosides is preferred (effective & safe) over multiple-daily dose. ➲ Tobramycin can be administered by **nebulizer for chronic pulmonary Ps. aeruginosa infection in cystic fibrosis** (300 mg every 12 hours for 28 days inhalation of nebulised solution)

Cotrimoxazole: Trimethoprim-sulfamethoxazole (TMP/SMX)

Mechanism of action	Inhibition of bacterial folic acid synthesis → inhibits DNA synthesis. Both are bacteriostatic but become bactericidal when combined (sequential block of folate synthesis)
Spectrum of activity	➲ A wide variety of aerobic gram-positive and gram-negative bacteria, and some protozoa. ➲ Chlamydia trachomatis ➲ Nocardia asteroides ➲ Shigella ➲ Salmonella ➲ Empiric treatment for simple UTI ➲ Prophylaxis and treatment of Pneumocystis jirovecii ➲ Prophylaxis of toxoplasmosis (Toxoplasma gondii)
Adverse reactions	➲ GI effects (nausea, vomiting) ➲ Skin (rash and pruritus) ➲ Nephrotoxicity (especially acute tubulointerstitial nephritis) ➲ Neutropenia, Agranulocytosis (more likely to occur in patients with HIV and elderly) ➲ Triggers hemolytic anemia in G6PD-deficient patients ➲ Drug interactions due to CYP450 inhibition
Contraindications	➲ Pregnancy and breastfeeding (in 1st trimester, trimethoprim → neural tube defects. In 3rd trimester, sulfonamides →↑free unconjugated bilirubin→ kernicterus in the neonate
Route of elimination	Primarily renal (via tubular secretion)
Mechanism of resistance	➲ Mutation in bacterial dihydropteroate synthase
Special notes	➲ The dose of TMP-SMX should be reduced for patients with creatinine clearance ≤30 mL per minute.

Beta-lactamase inhibitors

Overview

- β-lactamases usually produced by gram-negative and anaerobic organisms → split the β-lactam ring → ineffective β-lactam antibiotics.
- β-lactamase inhibitors → prevent the destruction of β-lactam antibiotics by β-lactamases →↑ spectrum of the antibiotic activity.
- Clavulanate, sulbactam, tazobactam, and avibactam are **beta-lactamase inhibitors** that have little intrinsic antibacterial activity but inhibit the activity of a number of plasmid-mediated beta-lactamases. A combination of one of these agents with ampicillin, amoxicillin, piperacillin, or ceftazidime enhanced the activity against many, but not all, organisms containing plasmid-mediated beta-lactamases.

Comparison of Antibiotic-Beta-Lactamase Inhibitor Combinations

Beta-Lactamase Inhibitor Combinations	Notes
Amoxicillin-clavulanate	➲ most strains of oxacillin-susceptible Staphylococcus aureus and beta-lactamase producing Haemophilus influenzae ➲ some beta-lactamase-producing Enterobacterales ➲ Used for otitis media, sinusitis, lower respiratory infections, bite wounds, and urinary tract infections.
Ampicillin-sulbactam	➲ many strains of Acinetobacter baumannii. ➲ most strains of S. aureus and beta-lactamase producing H. influenzae, some Enterobacterales, and anaerobes (including Bacteroides fragilis). ➲ used to treat patients with diabetic foot ulcers. Oral form: (sultamicillin tosylate): 375 to 750 mg two to three times daily
Piperacillin-tazobactam	➲ beta-lactamase producing S. aureus, H. influenzae, Neisseria gonorrhoeae, some Enterobacterales, and anaerobes (including B. fragilis) **Pseudomonas aeruginosa (require a dose at 4.5 g every six hours for normal renal function)**
Ceftazidime-avibactam	➲ most Enterobacterales (including those that produce AmpC beta-lactamase, **ESBL**, and some K. pneumoniae and OXA-type carbapenemases) **P. aeruginosa species with high MICs to ceftazidime alone.**

Beta-lactams antibiotics

Definition: a group of antibiotics that contains beta-lactam ring in their molecular structure and includes penicillins, carbapenems, monobactams, and cephalosporins.

Mechanism of action: Inhibit cell wall synthesis by blocking peptidoglycan crosslinking

Cephalosporins

Mechanism of action	Inhibit bacterial protein synthesis by binding to the penicillin-binding proteins (PBP) (transpeptidases) and prevent cell wall cross-linking (bactericidal effect), beta-lactam antibiotics.
Agents	➲ 1st generation: cephalexin (oral), cefazolin (IV, IM) ➲ 2nd generation: cefaclor (oral) cefuroxime (oral & IV) ➲ 3rd generation: cefixime, cefpodoxime (oral), ceftriaxone, cefotaxime, ceftazidime (IV) ➲ 4th generation: IV cefepime ➲ 5th generation: IV ceftaroline
Spectrum of activity	➲ Active against most gram-positive organisms and some gram-negative ➲ Ceftazidime and Cefepime has activity against Pseudomonas ➲ Ceftaroline, has activity against MRSA. It is not active against ESBL, *P. aeruginosa*, *Acinetobacter baumannii*, or *Bacteroides fragilis*.
Adverse reactions	➲ GI effects
Contraindications	➲ Known hypersensitivity
Route of elimination	Renal
Mechanism of resistance	➲ Inactivation by cephalosporinase (a type of β-lactamase) ➲ Change in transpeptidase (PBP) structure
Special notes	➲ All of the cephalosporins except ceftriaxone require dose modification in the presence of severe renal failure. ➲ Cephalosporins are safe in penicillin allergy if it is only a rash.

Carbapenems

Mechanism of action	Like penicillins, beta-lactam antibiotics, bind to bacterial transpeptidase, inhibit cross-linking of the bacterial cell wall synthesis (bactericidal effect).
Agents	➲ V imipenem (combined with cilastatin) ➲ IV meropenem ➲ IV ertapenem ➲ IV doripenem
Spectrum of activity	➲ Gram-positive cocci (except for MRSA and Enterococcus faecalis and Enterococcus faecium, which are intrinsically resistant) ➲ Gram-negative rods, including Pseudomonas aeruginosa (except ertapenem which has limited activity against Pseudomonas) ➲ Anaerobes ➲ Used for life-threatening infections after other drugs have failed ➲ Meropenem is useful for bacterial meningitis and intra-abdominal infection.
Adverse reactions	➲ CNS toxicity: can lower seizure threshold (highest risk: imipenem, lowest risk: meropenem)
Contraindications	➲ Imipenem is contraindicated in CNS infections due to seizure potential.
Route of elimination	Renal
Mechanism of resistance	➲ Beta-lactamase (penicillinase), a bacterial enzyme that can deactivate penicillins by cleaving the beta-lactam ring. Most common type of resistance ➲ Carbapenemases (cleave carbapenems) produced by K. pneumoniae, E. coli, and E. aerogenes ➲ Altered Penicillin-binding protein (PBP)
Special notes	➲ Imipenem is always given with cilastatin, which inhibits human dehydropeptidase I (a renal tubular enzyme that breaks down imipenem).

Vancomycin

Mechanism of action	Binds to **D-Ala-D-Ala** portion of the bacterial cell wall and blocks glycopeptide polymerization; inhibits cell wall synthesis (bactericidal effect).
Dose	➲ Loading dose: 20 to 35 mg/kg (based on actual body weight). Maximum 2 grams per dose) ➲ Initial maintenance dose: 15 to 20 mg/kg (rounded to the nearest 250 mg)
Spectrum of activity	➲ Gram-Positive Bacterial Infections, aerobic and anaerobic bacteria. ➲ used for initial therapy when MRSA is suspected. ➲ Administered orally for treatment of Clostridioides difficile
Adverse reactions	➲ Flushing (Red Man syndrome): mediated by histamine (pseudo-allergic reaction). Preventable with pre-treatment with antihistamines and slow infusion rate. ➲ Nephrotoxicity ➲ Ototoxicity ➲ Thrombophlebitis
Contraindications	➲ Imipenem is contraindicated in CNS infections due to seizure potential.
Route of elimination	Renal
Mechanism of resistance	➲ Amino acid modification of D-Ala-D-Ala to D-Ala-D-Lac
Special notes	➲ **Doses of 1g should be administered over at least 60 minutes.** ➲ **Vancomycin requires plasma level monitoring** (after three or four doses if the renal function is normal, or earlier if renal impairment is present) ➲ Following loading dose start maintenance dose according to GFR level: after 12 hours (if GFR ≥ 40mL/min), and after 24 hours (if GFR = 20-39 mL/min). If GFR < 20mL/min → check trough level 24 hours after loading dose; wait for trough result prior to re-dosing. ➲ The best determinant of vancomycin efficacy is the AUC/MIC (A 24-hour AUC/MIC of 400 or more is the target for clinical success). AUC/MIC means: ratio of Area Under the Curve (plasma concentration vs time) to Minimum Inhibitory Concentration. ➲ For practical reasons, a trough (pre-dose) plasma concentration is used as a surrogate measure of efficacy. Trough level means: a serum vancomycin level taken at the end of the dosing interval, approximately one hour prior to next dose. ➲ the target vancomycin trough level for the treatment of (MRSA) bacteremia is **15** to **20** µg/ml to achieve an AUC/MIC of 400. ➲ The trough level toxic threshold (30 mg/l). **If trough level > 30 mg/l → Omit dose and restart when level <15 mg/l.**

Spectrum of the drug – MEC
• **M** – MRSA • **E** – Enterococcus • **C** - Cl. difficle

Side effects – RON
• **R** - Red man syndrome • **O** – Ototoxicity • **N** - Nephrotoxicity

Linezolid

Mechanism of action	Binds to **50S** subunit of bacterial ribosomes and inhibits bacterial protein synthesis (bacteriostatic).
Dose	➲ IV or oral: 600 mg every 12 hours for 10–14 days.
Spectrum of activity	➲ Gram-positive species including MRSA and Vancomycin-resistant Enterococci (VRE) Infection. ➲ Used in multiple-drug regimens for treatment of multidrug-resistant (MDR) tuberculosis ➲ Usually used as a last-resort for multi-drug resistant infections
Adverse reactions	➲ Bone marrow suppression (anemia, leukopenia, and thrombocytopenia are common) ➲ Neuropathy (optic neuritis and peripheral neuropathy) ➲ Serotonin syndrome (due to partial monoamine oxidase (MAO) inhibition). ↑risk if compounded with other serotonergic drugs (e.g. MAOIs, SSRIs)
Contraindications	➲ Current or recent (within the last 2 weeks) use with monoamine oxidase inhibitors (MAOI) and selective serotonin reuptake inhibitors (SSRIs) ➲ Tyramine diet (a natural monoamine produced by the breakdown of tyrosine in food, includes: aged cheeses, processed meats e.g. dried sausages , hot dogs, and pickled or fermented vegetables)
Route of elimination	Renal
Mechanism of resistance	➲ Mutation of ribosomal RNA changes 50S binding site
Special notes	➲ Dosage adjustments not needed for hepatic or renal hepatic impairment.

Antiviral agents

Drug	Mechanism of action	Indications	Adverse effects/toxicity
Aciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn **inhibits the viral DNA polymerase**	HSV, VZV	Crystalline nephropathy
Ganciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn **inhibits the viral DNA polymerase**	CMV	Myelosuppression/agranulocytosis
Ribavirin	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, **interferes with the capping of viral mRNA**	Chronic hepatitis C, RSV	Haemolytic anaemia
Amantadine	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech
Oseltamivir	Inhibits neuraminidase	Influenza	
Foscarnet	Pyrophosphate analog which inhibits viiral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnasaemia, seizures
Interferon-α	Human glycoproteins which **inhibit synthesis of mRNA**	Chronic hepatitis B & C, hairy cell leukaemia	Flu-like symptoms, anorexia, myelosuppression
Cidofovir	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir)	CMV retinitis in HIV	Nephrotoxicity

Anti-fungal

Drug	Indications	Dose	Side Effects	Contraindications
Fluconazole	Candida infections (vaginal, oropharyngeal, systemic), cryptococcal meningitis	150 mg orally once for vaginal candidiasis, 200-400 mg/day for systemic infections	Nausea, vomiting, headache, liver dysfunction	Hypersensitivity to azoles, severe liver disease
Itraconazole	Histoplasmosis, blastomycosis, aspergillosis, onychomycosis	100-200 mg orally twice daily	Nausea, heart failure, liver toxicity, hypokalemia	Heart failure, severe liver disease, pregnancy
Amphotericin B	Severe systemic mycoses (e.g., invasive aspergillosis, cryptococcal meningitis)	0.5-1.5 mg/kg/day IV depending on infection severity	Nephrotoxicity, hypokalemia, fever, chills, hypotension	Severe renal impairment, hypersensitivity
Voriconazole	Invasive aspergillosis, Candida infections, Fusarium infections	6 mg/kg IV loading dose, then 4 mg/kg IV daily	Visual disturbances, hepatotoxicity, QT prolongation	Co-administration with certain drugs (e.g., rifampin), liver disease
Caspofungin	Invasive candidiasis, Aspergillus infections, febrile neutropenia	50 mg IV daily	Hepatotoxicity, fever, hypotension, anemia	Severe liver disease, hypersensitivity
Terbinafine	Dermatophytic infections (e.g., tinea pedis, onychomycosis)	250 mg orally once daily for 6-12 weeks	Headache, gastrointestinal upset, hepatotoxicity	Severe liver disease, pregnancy

Toxicology

Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Treatment
Paracetamol	▪ activated charcoal if ingested < 1 hour ago ▪ N-acetylcysteine (NAC) ▪ liver transplantation
Salicylate	▪ urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning ▪ haemodialysis
Opioid/opiates	Naloxone
Benzodiazepines	Flumazenil
Tricyclic antidepressants	• IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity ▪ arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias ▪ dialysis is ineffective in removing tricyclics
Lithium	▪ mild-moderate toxicity may respond to volume resuscitation with normal saline ▪ haemodialysis may be needed in severe toxicity ▪ sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion
Warfarin	Vitamin K, prothrombin complex
Heparin	Protamine sulphate
Beta-blockers	▪ if bradycardic then atropine ▪ in resistant cases glucagon may be used

Toxin	Treatment
Ethylene glycol	▪ works by competing with ethylene glycol for the enzyme alcohol dehydrogenase ▪ this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning ▪ **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol ▪ haemodialysis also has a role in refractory cases
Methanol poisoning	▪ fomepizole or ethanol ▪ haemodialysis
Organophosphate insecticides	▪ atropine ▪ the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit
Digoxin	Digoxin-specific antibody fragments
Iron	Desferrioxamine, a chelating agent
Lead	Dimercaprol, calcium edetate
Carbon monoxide	▪ 100% oxygen ▪ hyperbaric oxygen
Cyanide	Hydroxocobalamin also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate
Sarin (organophosphorus)	**Pralidoxime** → reactivates acetyl cholinesterase enzyme. It should be used in the first few hours.

Toxic alcohol poisoning

	Methanol	Isopropyl alcohol	Ethylene glycol
Sources	a slightly sweet-tasting alcohol that is commonly used as a solvent and gasoline additive. Ingested as ethanol substitute	a bitter-tasting alcohol with a fruity odor. It is used as a solvent and is the main component of rubbing alcohol. Used as disinfectants (e.g., rubbing alcohol), solvents or antifreeze	a sweet-tasting alcohol that is commonly used as an antifreeze agent. Ingested as ethanol substitute.
Mechanism of toxicity	Hepatic metabolism of methanol → accumulation of formaldehyde and formic acid → anion gap metabolic acidosis → cellular toxicity	Directly toxic; metabolized in the liver to acetone	➲ Hepatic metabolism of ethylene glycol → accumulation of glycolic acid → anion gap metabolic acidosis ➲ Metabolism of glycolic acid → accumulation of oxalic acid → deposition of calcium oxalate crystal in renal tubules → acute kidney injury
Features	➲ Features of alcohol intoxication (e.g., altered mental status, nausea) ➲ Ophthalmologic: optic neuropathy (e.g., blurred vision, scotoma, blindness), papilledema ➲ Cardiopulmonary: Kussmaul breathing, tachycardia ➲ GI: abdominal pain, hemorrhagic gastritis.	➲ Features of alcohol intoxication (e.g., altered mental status, ataxia) ➲ GI symptoms: abdominal pain, vomiting, hemorrhagic gastritis and/or hematemesis ➲ Cardiopulmonary (if aspirated): pulmonary edema ➲ Neurological: hypotonia, seizures	➲ Neurologic stage (first 12 hours after ingestion): altered mental status, ataxia, seizures. Nystagmus. ➲ Cardiopulmonary stage (12–24 hours after ingestion): Tachypnea secondary to metabolic acidosis, tachycardia, ARDS and/or circulatory collapse. ➲ Renal stage (24–72 hours after ingestion): flank pain, hematuria, oliguria or anuria, symptoms of hypocalcemia

	Methanol	Isopropyl alcohol	Ethylene glycol
Diagnosis	➲ serum methanol level > 50 mg/dL ➲ ↑osmolar gap: > 20 mOsm is highly suspicious for toxic alcohol ingestion. [4] ➲ Anion gap metabolic acidosis (e.g., ↓ pH, ↓ HCO3-)	➲ serum isopropyl alcohol levels > 50 mg/Dl ➲ ↑osmolar gap: > 20 mOsm ➲ **Absence of anion gap metabolic acidosis** ➲ Ketosis: urine and/or serum ketones	➲ serum ethylene glycol level > 50 mg/dL ➲ ↑osmolar gap: > 20 mOsm. ➲ Anion gap metabolic acidosis (e.g., ↓ pH, ↓ HCO3-) ➲ Urinalysis: hematuria, proteinuria, calcium oxalate crystalluria
Management	➲ **Antidote** for toxic alcohol poisoning (fomepizole): fomepizole (15 mg/kg IV once, then 10 mg/kg IV every 12 hours) ➲ **Vitamin supplementation:** Thiamine (100 mg IV daily) + Pyridoxine (100 mg IV daily) ➲ **Hemodialysis:** in patient with neurological symptoms (e.g., seizures, coma, new vision deficits), AKI	➲ **Supportive care** ➲ Antidotes for toxic alcohol poisoning are not required	➲ **Antidote:** fomepizole. ➲ **Vitamin supplementation:** Thiamine + Pyridoxine ➲ **Acidosis:** IV sodium bicarbonate bolus and infusion (1–2 mEq/kg IV once, followed by infusion of D5W with 150 mL of 8.4% sodium bicarbonate per liter IV at 1.5–2 times maintenance rate) until pH normalizes. ➲ **Hemodialysis** in patients with: Neurologic symptoms (e.g., coma, seizures), acute kidney injury.

Ecstasy (MDMA) poisoning

Definition

- Ecstasy is an amphetamine derivative (MDMA, 3,4-**M**ethylene-**D**ioxy-**M**eth-**A**mphetamine) use became popular in the 1990's during the emergence of dance music culture
- is a semi-synthetic hallucinogen used as a recreational drug.

Features

- Neurological: agitation, delirium, anxiety, confusion, ataxia
- Cardiovascular: tachycardia, hypertension
- **Hyponatraemia**
- Hyperventilation
- **Hyperthermia**

Complications

- Intracranial hemorrhage, seizure
- Myocardial infarction, aortic dissection
- Disseminated intravascular coagulation
- Serotonin syndrome
- Rhabdomyolysis

Management: supportive (no specific antidote)

- **Hyperthermia:** Cold intravenous fluids if the core temperature is over 39 °C. Dantrolene may be used and/or paralysis and ventilation if simple measures fail.
- **Severe hypertension and psychomotor agitation:** benzodiazepines (eg, lorazepam, 1 to 2 mg IV push; repeat until hypertension is controlled or the patient is sedated). Avoid beta-blockers in the treatment of acute sympathomimetic poisoning.
- **Severe symptomatic hyponatremia** (serum sodium usually less than 120 meq/L (mmol/L)): hypertonic saline (3%).

Opioid Toxicity

Aspect	Details
Definition	Opioid toxicity occurs when excessive opioids suppress the central nervous system, causing life-threatening symptoms, including respiratory depression.
Common Causes	- Overdose (accidental or intentional) - Polypharmacy (e.g., with benzodiazepines or alcohol) - Renal or liver impairment reducing drug clearance - Chronic opioid use with tolerance changes
Common Offending Drugs	- Morphine - Fentanyl - Oxycodone - Codeine - Methadone - Heroin

Clinical Features

System	Findings
CNS	- Decreased level of consciousness - Lethargy or coma - Slurred speech - Pupillary constriction (miosis)
Respiratory	- Respiratory depression (slow or shallow breathing) - Hypoxia - Cyanosis
Cardiovascular	- Hypotension - Bradycardia
Gastrointestinal	- Constipation - Nausea and vomiting
Others	- Hypothermia - Decreased response to stimuli

Investigations and Findings

Investigation	Findings
Arterial blood gas	Respiratory acidosis, hypoxia
Toxicology screen	Positive for opioids or mixed substances
ECG	Prolonged QT interval (with methadone)
Blood glucose	Hypoglycaemia (important differential to exclude)

Complications

Complication	Details
Respiratory failure	Leading cause of death in overdose
Aspiration pneumonia	Due to vomiting and decreased consciousness
Rhabdomyolysis	From prolonged immobilization
Pulmonary oedema	Non-cardiogenic, may develop post-Naloxone
Seizures	Especially with tramadol or meperidine toxicity

Management

Intervention	Details
Airway and breathing	- Maintain airway and provide oxygen - Mechanical ventilation if severe respiratory depression
Naloxone (opioid antagonist)	**Dose**: 0.4–2 mg IV, repeat every 2–3 minutes as needed (max 10 mg) - Continuous infusion for long-acting opioids
Activated charcoal	If ingestion occurred within 1 hour (for oral overdose)
IV fluids	To manage hypotension
Treat complications	- Monitor for pulmonary oedema, hypothermia, and seizures

Features of opioid misuse

- needle track marks
- yawning, lacrimation, rhinorrhoea
- drowsiness, hallucinations, **myoclonus** and delirium.
- pinpoint pupils
- respiratory depression
- sharing needles complications: HIV, hepatitis B & C

Management

- **Emergency opioid overdose:** IV **naloxone** (0.4 mg), repeated up to a total dose of 2 mg depending on clinical response. **(as the half-life of naloxone is shorter than that of opioids).**
- **Opioid dependence**
  - ⇨ Detoxification: NICE recommend methadone or buprenorphine as the first-line treatment in opioid detoxification. detoxification should normally last up to 4 weeks in an inpatient/residential setting and up to 12 weeks in the communit
  - ⇨ compliance is monitored using urinalysis
  - ⇨ **Naltrexone is a long-acting opioid antagonist can be used to prevent relapse in detoxified patients who were formerly dependent on opioids.**

- **Symptomatic treatment:**
  - ⇨ **Opioid-induced nausea:** 1st line: dopamine antagonist, (prochlorperazine or metoclopramide) or a serotonin receptor antagonist (ondansetron)
  - ⇨ **Opioid-induced constipation (the most common and persistent side effect of chronic opioid use):** senna
  - ⇨ **Myoclonus:** clonazepam 0.5 mg orally every six to eight hours, lorazepam 0.5 to 1 mg every two to three hours

Opioid withdrawal

- **Features**
  - ⇨ Flu-like symptoms – Lacrimation, rhinorrhea, diaphoresis, shivering, fever
  - ⇨ Mydriasis (pupillary dilatation), mild hypertension, tachycardia, anxiety and irritability, insomnia, yawning, agitation.
  - ⇨ Abdominal cramps, diarrhea, nausea, and/or vomiting
- **Treatment:** medically supervised opioid withdrawal (detoxification)
  - ⇨ **1st line:** buprenorphine (Opioid Partial Agonist): subcutaneous 16 mg (weekly), followed by an additional 8 mg (weekly) within 3 days of the initial dose for a total recommended weekly dose of 24 mg. Since **buprenorphine is a <u>partial</u> agonist at opioid receptors, it will antagonise the action of a <u>full</u> agonist such as morphine.**
  - ⇨ **2nd line:** methadone Initially give 10 mg of methadone syrup and wait about 60 min to determine its effect. Continue administering in 10 mg doses until symptoms are under control. It is rare to exceed a total dose of 40 mg over 24 hours.

Lead poisoning

> **Along with acute intermittent porphyria, lead poisoning should be considered in patients with a combination of abdominal pain and neurological signs**

Common sources of lead exposure

- Contaminated water from old lead water pipes
- Occupation such as Painter, Plumbers, Construction workers, Battery manufacturers
- Pica (an abnormal desire to eat substances)
- Lead can also be absorbed through the skin and by inhalation.

Pathophysiology

- inhibition of aminolevulinate dehydratase and ferrochelatase → heme synthesis disruption → ↑ protoporphyrin and ↑ aminolevulinic acid in RBCs

Features

- Abdominal pain, nausea, constipation
- Peripheral neuropathy (mainly motor) due to demyelination
- Anaemia , Fatigue, joint/muscle aches
- Headaches, difficulty concentrating, short-term memory deficits, and irritability.
- Hypertension
- Blue lines on gum margin (only 20%)

Features and complications of lead poisoning:

➲ **Anemia, Basophilic stippling, Constipation, Demyelination, Encephalopathy, Foot drop, Gum deposition/Growth retardation/Gout,**

Diagnosis

- Diagnostic test: blood lead levels: >10 µg/dL
- Abdominal radiographs (to see if there is any unabsorbed lead, which can be removed by whole-bowel irrigation)
- CBC: microcytic anaemia. Blood film shows **basophilic stippling** (due to accumulation of RNA in the RBCs due to inhibition of pyrimidine 5 nucleotidase by lead) (clover-leaf morphology)

Management: chelating agents (in patients with blood lead levels ≥45 mcg/dL)

- Severe poisoning without encephalopathy (blood lead level >70 mcg/dL): succimer + IV or IM calcium disodium edetate (CaNa2 EDTA)
- Severe poisoning with encephalopathy (blood lead level >70 mcg/dL): IM dimercaprol + calcium disodium edetate (CaNa2 EDTA)
- Mid poisoning (blood lead level 45 - 70 mcg/dL):
  - ⇨ 1st line: Succimer (Dimercaptosuccinic acid) [DMSA] 10 mg/kg three times per day for five days, followed by 10 mg/kg twice per day for two weeks.
  - ⇨ 2nd line: oral penicillamine

Paracetamol overdose

Definition

- **Paracetamol (Acetaminophen) overdose** occurs when excessive amounts are ingested, leading to potentially life-threatening liver toxicity.

Pathophysiology

- **Normal metabolism**: Paracetamol is primarily metabolised in the liver via glucuronidation and sulphation.
- In overdose, these pathways are saturated, and more paracetamol is converted to **NAPQI** (a toxic metabolite).
- **NAPQI** is usually detoxified by **glutathione.** In overdose, glutathione stores are depleted, leading to liver cell damage.

Risk Factors for Toxicity

1. **High-dose ingestion** (> 7.5g in adults or > 150mg/kg in children).
2. **Chronic alcohol use**: Depletes glutathione and increases NAPQI production.
3. **Malnutrition** or **fasting**: Low glutathione stores.
4. **Enzyme inducers** (e.g., anticonvulsants like phenytoin).

Clinical Features

- **Early phase (0-24 hours)**: Asymptomatic or non-specific symptoms like nausea, vomiting, lethargy, and malaise.
- **Middle phase (24-72 hours)**: Right upper quadrant pain, elevated liver enzymes (ALT, AST), jaundice.
- **Late phase (72-96 hours)**: Signs of **hepatic necrosis**, including coagulopathy, hypoglycaemia, jaundice, and encephalopathy. Potential progression to **acute liver failure** and **multi-organ failure.**
- **Recovery phase (4-14 days)**: Resolution of symptoms if liver damage does not progress.

Investigations

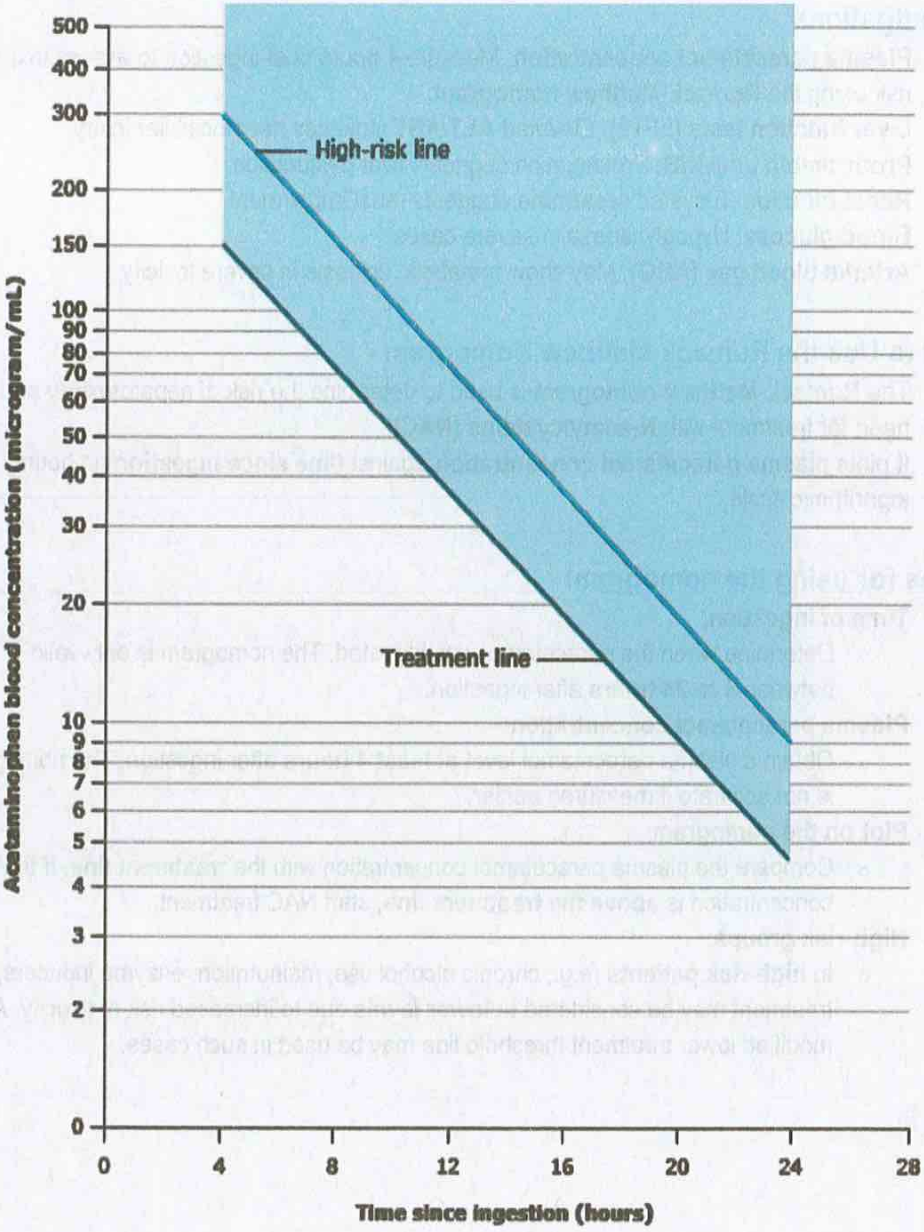
- **Plasma paracetamol concentration**: Measure 4 hours post-ingestion to assess toxicity risk using the **Rumack-Matthew nomogram**.
- **Liver function tests (LFTs)**: Elevated **ALT/AST** indicates hepatocellular injury.
- **Prothrombin time/INR**: Prolongation suggests liver dysfunction.
- **Renal function**: Elevated **creatinine** suggests renal impairment.
- **Blood glucose**: Hypoglycaemia in severe cases.
- **Arterial blood gas (ABG)**: May show metabolic acidosis in severe toxicity.

How to Use the Rumack-Matthew Nomogram

- The **Rumack-Matthew nomogram** is used to determine the risk of hepatotoxicity and the need for treatment with **N-acetylcysteine (NAC)**.
- It plots **plasma paracetamol concentration** against **time since ingestion** (in hours) on a logarithmic scale.

Steps for using the nomogram:

1. **Time of ingestion**:
   - Determine when the paracetamol was ingested. The nomogram is only valid between **4 to 24 hours** after ingestion.
2. **Plasma paracetamol concentration**:
   - Obtain a plasma paracetamol level **at least 4 hours** after ingestion. The nomogram is not accurate if measured earlier.
3. **Plot on the nomogram**:
   - Compare the plasma paracetamol concentration with the **treatment line**. If the concentration is **above the treatment line**, start NAC treatment.
4. **High-risk groups**:
   - In **high-risk patients** (e.g., chronic alcohol use, malnutrition, enzyme inducers), treatment may be considered at **lower levels** due to increased risk of toxicity. A modified lower treatment threshold line may be used in such cases.


500
400
300
200
150
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
0
High-risk line
Treatment line
Acetaminophen blood concentration (microgram/mL)
0
4
8
12
16
20
24
28
Time since ingestion (hours)

Management

1. **Activated charcoal** (within 1 hour of ingestion):
   - Dose: **50g** orally for adults (reduces absorption of paracetamol).
2. **N-acetylcysteine (NAC)**: Antidote to prevent liver damage by replenishing **glutathione** stores.
   - Start NAC if plasma paracetamol levels cross the treatment line on the **Rumack-Matthew nomogram**.
   - **IV NAC regimen** (in the UK): **300 mg/kg body weight over 21-hour in** 3 consecutive doses, diluted in glucose (preferably) or 0.9% sodium chloride
     - **1st infusion**: 150 mg/kg over 1 hour.
     - **2nd infusion**: 50 mg/kg over 4 hours.
     - **3rd infusion**: 100 mg/kg over 16 hours.
   - Oral NAC is an alternative where IV access is difficult.

	1st infusion	2nd infusion	3rd infusion
Drug dose	150 mg/kg	50 mg/kg	100 mg/kg
Infusion fluid	200 ml	500 ml 5	1000 ml
Duration of infusion	1 hour	4 hours	16 hours

3. **Supportive care**:
   - Monitor **LFTs**, **INR**, **renal function**, **glucose levels**, and **acid-base status**.
   - Treat **hypoglycaemia** or **coagulopathy** as needed.
   - **Haemodialysis**: Rarely used, only in severe cases of acidosis or multi-organ failure.
4. **Liver transplant**: Consider in severe acute liver failure based on **King's College Criteria**:
   - pH < 7.3 or
   - **INR > 6.5** with **creatinine > 300 µmol/L** and **grade III or IV hepatic encephalopathy**.

Prognosis

- Early administration of NAC within 8 hours of ingestion is highly effective and prevents serious liver damage.
- Delay in treatment beyond 8 hours increases the risk of **acute liver failure** and death.

Key Points

- **Paracetamol overdose** is the most common cause of acute liver failure in the UK.
- Prompt treatment with **N-acetylcysteine** (NAC) is critical for preventing severe hepatotoxicity.
- Use the **Rumack-Matthew nomogram** to assess the need for NAC based on plasma paracetamol levels.

Salicylate Overdose

Clinical Features

- **Early Symptoms**: Tinnitus, nausea, vomiting, hyperventilation, and respiratory alkalosis.
- **Progression**: Metabolic acidosis, hyperthermia, confusion, seizures, and potentially coma.

Management Overview

1. **Initial Assessment**:
   - **History and Examination**: Determine the amount and timing of salicylate ingestion.
   - **Laboratory Investigations**: Measure plasma salicylate concentration, arterial blood gases, electrolytes, renal function, and glucose levels.

2. **Decontamination**:
   - **Activated Charcoal**: Administer if the patient presents within 1 hour of ingestion of more than 120 mg/kg of salicylate, provided there are no contraindications such as reduced consciousness without airway protection.
3. **Supportive Care**:
   - **Fluid Resuscitation**: Address dehydration with intravenous fluids, typically 0.9% sodium chloride.
   - **Electrolyte Correction**: Monitor and correct hypokalaemia, aiming for plasma potassium levels of 4–4.5 mmol/L.
4. **Enhanced Elimination**:
   - **Urinary Alkalinisation**:
     - Consider in patients with plasma salicylate concentrations >500 mg/L (3.6 mmol/L).
     - Administer intravenous sodium bicarbonate to achieve a urine pH of 7.5–8.5, enhancing salicylate excretion.
     - Ensure serum potassium is within the normal range before initiating.
5. **Haemodialysis**:
   - **Indications**:
     - Severe poisoning characterized by plasma salicylate concentrations >700 mg/L (5.1 mmol/L).
     - Metabolic acidosis resistant to treatment, acute renal failure, pulmonary oedema, or neurological impairment (e.g., coma, seizures).
     - Patients at increased risk (age <10 or >70 years).

Organophosphate insecticide poisoning

Mechanism

- Organophosphate is an anticholinesterase, thus organophosphate poisoning → inhibition of acetylcholinesterase → accumulation of acetylcholine at muscarinic receptors, nicotinic receptors and in the central nervous system

Features (mnemonic = SLUD)

- **S**alivation
- **L**acrimation
- **U**rination
- **D**efecation/**d**iarrhoea
- Bronchorrhea, bronchospasm
- CVS: hypotension, bradycardia
- CNS: Small pupils (**miosis**), muscle fasciculation, tremor, Organophosphate-induced neuropathy (develop 2 weeks after exposure with flaccid paralysis initially and spastic paralysis later)

Management

- **Atropine:** 2 to 5 mg IV (0.05 mg/kg). If no effect is noted, the dose is doubled every 3 - 5 minutes until pulmonary muscarinic signs and symptoms are alleviated. Atropine does not bind to nicotinic receptors, it is ineffective in treating neuromuscular dysfunction.
- **Pralidoxime** (cholinesterase reactivating agent, effective in treating both muscarinic and nicotinic symptoms): 30 mg/kg IV slowly over 30 minutes. Pralidoxime should not be administered without concurrent atropine due to transient oxime-induced acetylcholinesterase inhibition.
- **Benzodiazepine:** for organophosphate-induced seizures. Prophylactic diazepam (eg, 10 mg IV) can decrease neurocognitive dysfunction

Miscellaneous

Antihistamines

Action: histamine h1-receptor antagonists

Indication: Allergic rhinitis, Urticaria.

Classification

	1st generation	2nd generation
Agents	Diphenhydramine Chlorpheniramine Hydroxyzine	**Cetirizine** (10 mg once daily) **Levocetirizine** (an active metabolite of cetirizine): (5 mg once daily) **Loratadine** (long-acting, 10 mg once daily) Desloratadine (an active metabolite of loratadine, 5 mg once daily) **Fexofenadine** (180 mg daily)
Side effects	**CNS :** sedation because they are lipophilic and easily cross the blood-brain barrier. Confusion (older patients) **Anticholinergic:** Dry mouth and eyes, Impotence, urinary retention, Glaucoma Others: Weight gain, Prolonged QT interval	Minimally sedating due to poor CNS penetration (**cetirizine and levocetirizine are more sedating than loratadine and desloratadine,**)

Summary of Commonly Used Antihistamines

Drug	Dose	Uses	Avoid In
Loratadine	10 mg once daily	Allergic rhinitis, chronic urticaria	Severe liver impairment, hypersensitivity
Cetirizine	10 mg once daily	Allergic rhinitis, chronic urticaria	Severe renal impairment, hypersensitivity
Fexofenadine	120-180 mg once daily	Seasonal allergic rhinitis, chronic urticaria	Elderly with renal dysfunction, severe liver impairment
Chlorphenamine	4 mg every 4-6 hours	Seasonal allergies, allergic conjunctivitis, anaphylaxis adjunct	Narrow-angle glaucoma, elderly, urinary retention
Diphenhydramine	25-50 mg every 4-6 hours	Insomnia, motion sickness, allergic reactions	Elderly (risk of confusion), narrow-angle glaucoma, asthma
Hydroxyzine	25-100 mg up to 4 times daily	Anxiety, pruritus, allergic reactions	Pregnancy (1st trimester), QT prolongation risk
Promethazine	12.5-25 mg every 4-6 hours	Nausea, vomiting, motion sickness, insomnia	Children under 2 years (risk of respiratory depression)
Levocetirizine	5 mg once daily	Allergic rhinitis, chronic idiopathic urticaria	Severe renal impairment
Desloratadine	5 mg once daily	Allergic rhinitis, chronic urticaria	Severe renal or liver impairment

Key Considerations

- **Non-sedating antihistamines (e.g., loratadine, cetirizine, fexofenadine)** are preferred for daytime use.
- **Sedating antihistamines (e.g., diphenhydramine, chlorphenamine, promethazine)** are often used for insomnia or nausea but should be avoided in elderly due to the risk of confusion.

This Page Is Intentionally Left Blank

4th edition 2025

Notes & Notes

For MRCP

Part 1 & 2

By

Dr. Yousif Abdallah Hamad

Chapter -12

Basic science

IMMUNOLOGY

Immune System Response

Overview

The immune system is a complex network of cells, tissues, and organs that defend the body against harmful invaders like bacteria, viruses, and other pathogens. Its responses can be categorised into innate and adaptive immunity.

Innate Immune Response

- **Characteristics**: First line of defence; rapid but non-specific.
- **Components**:
  - **Physical Barriers**: Skin, mucous membranes, and cilia.
  - **Immune Cells**: Macrophages, neutrophils, natural killer (NK) cells, and dendritic cells.
  - **Proteins and Molecules**:
    - Complement system: Promotes pathogen clearance.
    - Cytokines: Mediate inflammation and recruit immune cells.
- **Mechanisms**:
  - Pathogen recognition through pattern recognition receptors (e.g., Toll-like receptors).
  - Inflammation to contain and eliminate pathogens.
  - Phagocytosis by neutrophils and macrophages.

Adaptive Immune Response

- **Characteristics**: Specific to pathogens; slower onset but develops memory.
- **Components**:
  - **Humoral Immunity (B cells)**:
    - B cells produce antibodies that bind to specific antigens on pathogens.
    - Neutralises pathogens or marks them for destruction by phagocytes or the complement system.
  - **Cell-Mediated Immunity (T cells)**:
    - **Helper T Cells (CD4+)**:
      - Modulate immune responses by releasing cytokines.
      - Activate B cells and cytotoxic T cells.
    - **Cytotoxic T Cells (CD8+)**:
      - Recognise and destroy infected or abnormal cells.

Th1 and Th2 Responses

- **Th1 Cells**:
  - Promote cell-mediated immunity, combating intracellular pathogens (e.g., viruses).
  - Involve cytokines like interferon-gamma (IFN-\u03b3).
- **Th2 Cells**:
  - Support humoral immunity and mediate responses to extracellular pathogens and allergens.
  - Involve cytokines like interleukin-4 (IL-4) and IL-5.
- **Balance**:
  - A balanced Th1/Th2 response is critical for effective immunity.
  - Imbalance may lead to immune-related conditions (e.g., Th2 dominance in allergic diseases).

Memory and Vaccination

- **Memory Cells**:
  - Adaptive immunity develops memory through memory B and T cells.
  - These cells enable rapid and robust responses upon re-exposure to the same pathogen.
- **Vaccination**:
  - Mimics infection to stimulate memory cell formation without causing disease.
  - Ensures faster and stronger immune responses during future encounters.

Comparison: Innate vs Adaptive Immunity

Feature	Innate Immunity	Adaptive Immunity
Onset	Immediate (minutes)	Delayed (days to weeks)
Specificity	Non-specific	Antigen-specific
Memory	Absent	Present
Key Players	Neutrophils, macrophages, NK cells	T cells, B cells
Pathogen Recognition	Pattern recognition receptors (e.g., TLRs)	Antigen receptors on T/B cells

Cells of the Immune System

The immune system consists of diverse cells that work together to defend against infections and maintain homeostasis. These cells are categorised into two main groups: **innate** and **adaptive** immune cells.

Innate Immune System Cells

1. **Neutrophils**:
   - Most abundant white blood cells.
   - First responders to infection sites; perform phagocytosis and release antimicrobial substances.
2. **Macrophages**:
   - Tissue-resident cells derived from monocytes.
   - Conduct phagocytosis and present antigens to T cells, linking innate and adaptive immunity.
3. **Dendritic Cells**:
   - Professional antigen-presenting cells (APCs).
   - Process antigens and activate T cells to initiate adaptive responses.
4. **Natural Killer (NK) Cells**:
   - Detect and destroy virus-infected and tumour cells by recognising changes in MHC class I molecules.
5. **Eosinophils and Basophils**:
   - Eosinophils: Combat multicellular parasites and release toxic granules.
   - Basophils: Mediate allergic reactions by releasing histamine and other substances.

Adaptive Immune System Cells

1. **B Lymphocytes (B Cells)**:
   - Produce antibodies targeting specific antigens.
   - Differentiate into plasma cells to neutralise pathogens and clear infections.

2. **T Lymphocytes (T Cells):**
   - **Helper T Cells (CD4+)**: Secrete cytokines to coordinate immune responses and activate B and cytotoxic T cells.
   - **Cytotoxic T Cells (CD8+)**: Destroy infected or cancerous cells by recognising antigens presented via MHC class I.
   - **Regulatory T Cells**: Maintain immune tolerance and suppress excessive immune activity to prevent autoimmunity.

Summary of Immune Cells and Functions

Cell Type	Origin	Function	Clinical Relevance
Neutrophils	Bone marrow	Phagocytosis, ROS production	Neutropenia increases infection risk
Macrophages	Monocytes	Phagocytosis, antigen presentation	Granulomas in TB, sarcoidosis
Dendritic Cells	Bone marrow	Antigen presentation to T cells	Impaired immunity if defective
NK Cells	Bone marrow	Destroy infected/tumour cells	Cancer surveillance
B Cells	Bone marrow	Antibody production, antigen presentation	Deficiencies lead to recurrent infections
T Cells	Thymus	Helper (CD4+) and cytotoxic (CD8+) functions	HIV targets CD4+ T cells
Eosinophils	Bone marrow	Parasitic defence, allergy mediation	Elevated in eosinophilic disorders

Cytokines and Interleukins

Cytokines

Cytokines are small proteins that act as signalling molecules within the immune system. They regulate immune responses, inflammation, and hematopoiesis. Produced by immune cells (lymphocytes, macrophages) and non-immune cells (endothelial cells, fibroblasts), cytokines are essential for communication between cells.

Key Functions

1. **Immune Response Modulation**:
   - Activate or inhibit immune cell functions to defend against pathogens.
2. **Inflammation Regulation**:
   - Initiate and resolve inflammatory processes, aiding in infection control and tissue repair.
3. **Cell Differentiation and Proliferation**:
   - Influence growth, differentiation, and survival of cells, including those involved in hematopoiesis.

Interleukins

Interleukins, a subgroup of cytokines, are primarily produced by leukocytes and play key roles in immune cell communication and regulation.

- **IL-1**: Promotes fever and immune cell activation during inflammation.
- **IL-2**: Stimulates T cell growth and differentiation; vital for adaptive immunity.

- **IL-4**: Encourages Th2 cell differentiation and enhances B cell proliferation and antibody production.
- **IL-6**: Has both pro-inflammatory and anti-inflammatory effects during infections and tissue injury.
- **IL-10**: Anti-inflammatory; limits immune responses to prevent host damage.

Clinical Significance

1. **Cytokine Storms**:
   - Excessive cytokine release can cause severe systemic inflammation, tissue damage, and life-threatening outcomes, as seen in infections and autoimmune diseases.
2. **Therapeutic Applications**:
   - **IL-2**: Used in cancer immunotherapy to boost immune cell activity.
   - **Interferons**: Employed to treat conditions like multiple sclerosis and hepatitis C.

Important Cytokines in Cellular Immunity

Cytokine	Function	Secreted by
Interleukin-1 (IL-1)	Causes fever and acute inflammation; activates endothelial adhesion molecule expression.	Macrophages
Interleukin-2 (IL-2)	Stimulates growth and survival of T-cells and NK cells.	All T-cells
Interleukin-3 (IL-3)	Stimulates growth and differentiation of bone marrow cells.	All T-cells
Interleukin-4 (IL-4)	Induces differentiation into Th2 cells; promotes B-cell growth and class switching to IgG and IgE.	Th2 cells
Interleukin-5 (IL-5)	Promotes B-cell and eosinophil growth; enhances class switching to IgA.	Th2 cells
Interleukin-6 (IL-6)	Stimulates fever and acute phase protein production in the liver.	Macrophages
Interleukin-8 (IL-8)	Stimulates neutrophil chemotaxis to infection sites.	Macrophages
Interleukin-10 (IL-10)	Inhibits inflammation by suppressing macrophages and dendritic cells; decreases MHC and Th1 cytokine expression.	Regulatory T-cells
Interleukin-12 (IL-12)	Promotes differentiation into Th1 cells; activates NK cells for cytotoxic activity.	Macrophages
Tumour Necrosis Factor-α (TNF-α)	Alters vascular endothelium to promote leakage; recruits WBCs to site; induces fever.	Macrophages
Interferon-α/β (IFN-α/β)	Activates antiviral defence, downregulates protein synthesis, and upregulates MHC expression.	All cells
Interferon-γ (IFN-γ)	Activates macrophages, enhances antigen presentation, promotes granuloma formation, and increases NK cell killing.	Th1 cells

Human Leukocyte Antigen (HLA)

Definition

The human leukocyte antigen (HLA) system is a group of genes encoding major histocompatibility complex (MHC) proteins. These proteins are critical for antigen presentation and immune system regulation.

Classes of HLA

1. **Class I HLA**:
   - Includes: HLA-A, HLA-B, HLA-C.
   - **Location**: Expressed on all nucleated cells (except erythrocytes and trophoblasts).
   - **Function**: Presents endogenous antigens (e.g., viral proteins) to CD8+ cytotoxic T cells.
   - **Clinical Relevance**: Key in organ transplant rejection and viral immunity.
2. **Class II HLA**:
   - Includes: HLA-DR, HLA-DQ, HLA-DP.
   - **Location**: Expressed on antigen-presenting cells (APCs) like macrophages, dendritic cells, and B cells.
   - **Function**: Presents exogenous antigens to CD4+ helper T cells.
   - **Clinical Relevance**: Plays a significant role in autoimmune diseases and transplant compatibility.

Clinical Significance of HLA

1. **Transplantation**:
   - HLA matching, especially HLA-DR, is crucial to prevent rejection.
   - HLA mismatches can lead to hyperacute or chronic rejection.
2. **Disease Associations**:
   - **HLA-B27**: Associated with ankylosing spondylitis, reactive arthritis.
   - **HLA-DR3/DR4**: Linked with type 1 diabetes mellitus.
   - **HLA-DQ2/DQ8**: Strongly associated with coeliac disease.
   - **HLA-DR2**: Associated with multiple sclerosis and systemic lupus erythematosus.

Key HLA Associations

HLA type	Associated diseases
HLA-A3	➲ Hemochromatosis
HLA-B5	➲ Behcet's disease HLA B51 is a split of B5
HLA-B47	➲ 21-hydroxylase deficiency
HLA-CW6	➲ Psoriasis
HLA-DR3 + DR4 combined	➲ Diabetes mellitus type 1(but more with HLA-DR4)
HLA-DR7	➲ steroid-responsive nephrotic syndrome
HLA-DR2	➲ Narcolepsy ➲ Goodpasture's ➲ hay fever, ➲ systemic lupus erythematosus, ➲ multiple sclerosis.
HLA-DR4	➲ **Felty's syndrome (90%)** → most common ➲ Rheumatoid arthritis (70%) ➲ Diabetes mellitus type 1 (> DR3) ➲ **Drug-induced SLE** ➲ IgA nephropathy ➲ HOCM
HLA-B27	➲ Ankylosing spondylitis ➲ Post-gonococcal arthritis ➲ Reiter's syndrome (reactive arthritis) ➲ Acute anterior uveitis
HLA-DR3	➲ Autoimmune hepatitis ➲ Primary biliary cirrhosis ➲ Coeliac disease (95% associated with HLA-DQ2) ➲ Diabetes mellitus type 1 ➲ Primary Sjögren syndrome ➲ Dermatitis herpetiformis

HLA (Human Leukocyte Antigen)

- HLA – structure and function
  - Class I molecule (HLA-A, B, C)
    - expressed on all nucleated cells
    - Presents endogenous Ag to T-lymphocyte (CD8+)
  - Class II molecule (HLA-DR, DQ, DP)
    - expressed on B lymphocyte, activated T lymphocyte, monocyte, macrophage, dendritic cells, etc.
    - Presents exogenous Ag to helper T-lymphocyte (CD4+)

MHC I-associated loci (HLA-A/-B/-C) only have 1 letter after the hyphen, while MHC II-associated loci (HLA-DR/-DP/-DQ) have 2 letters.

MRCP- part-1-2018: **Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection?**

➲ HLA-C

- Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection; specifically,
- HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant.

Cluster of Differentiation (CD Markers)

Definition

CD markers are cell surface molecules that help identify and classify immune cells based on their specific functions and stages of differentiation.

Key CD Markers and Their Functions

CD Marker	Function	Cell Type
CD4	Co-receptor for MHC class II; helper T cell marker	Helper T cells (Th cells)
CD8	Co-receptor for MHC class I; cytotoxic T cell marker	Cytotoxic T cells (CTLs)
CD14	Receptor for lipopolysaccharide (LPS)	Monocytes, macrophages
CD19/20	B cell differentiation and activation markers	B cells
CD25	IL-2 receptor alpha chain; regulatory T cell marker	Regulatory T cells, activated T cells
CD34	Marker for haematopoietic stem cells	Stem cells
CD56	Marker for natural killer (NK) cells	NK cells

Clinical Relevance

1. **Diagnosis**:
   - CD markers help identify immune cell populations in immunodeficiencies, leukaemias, and lymphomas (e.g., CD19+ B cell lymphoma).
2. **Therapeutics**:
   - Targeted therapies use CD markers (e.g., anti-CD20 for B-cell lymphomas and autoimmune diseases).
3. **Immune Monitoring**:
   - CD4 and CD8 counts are critical in monitoring HIV progression.

Immunoglobulins (Antibodies)

Definition

Immunoglobulins (antibodies) are glycoproteins produced by plasma cells in response to antigens. They play a critical role in humoral immunity by neutralising pathogens, enhancing phagocytosis, and activating the complement system.

Structure

1. **Fab Region**:
   - Binds specific antigens.
   - Composed of variable regions of light and heavy chains.
2. **Fc Region**:
   - Determines antibody class.
   - Mediates effector functions (e.g., complement activation, binding to Fc receptors).

Classes of Immunoglobulins

1. **IgG**:
   - **Abundance**: 75% of serum antibodies.
   - **Functions**:
     - Opsonisation and phagocytosis.
     - Activates complement (classical pathway).
     - Provides neonatal immunity (crosses placenta).
   - **Clinical Relevance**: Elevated in chronic infections and autoimmune diseases.
2. **IgA**:
   - **Abundance**: 15% of serum antibodies.
   - **Functions**:
     - Found in mucosal surfaces (e.g., respiratory, gastrointestinal).
     - Provides local immunity in secretions (e.g., saliva, tears, breast milk).
   - **Clinical Relevance**: Deficiency associated with recurrent respiratory and GI infections.
3. **IgM**:
   - **Abundance**: 10% of serum antibodies.
   - **Functions**:
     - First antibody produced in primary immune response.
     - Strong complement activator.
   - **Clinical Relevance**: Marker of recent infection (acute phase).
4. **IgE**:
   - **Abundance**: <0.1% of serum antibodies.
   - **Functions**:
     - Binds to allergens and triggers histamine release from mast cells.
     - Defends against parasitic infections.
   - **Clinical Relevance**: Elevated in allergic disorders and parasitic infections.
5. **IgD**:
   - **Abundance**: ~1% of serum antibodies.
   - **Functions**:
     - Found on the surface of naive B cells.
     - Plays a role in B cell activation.
   - **Clinical Relevance**: Limited clinical implications.

Summary of Immunoglobulins

Antibody	Frequency in Serum	Functions	Clinical Relevance
IgG	75%	Opsonisation, complement activation, neonatal immunity	Chronic infections, autoimmune diseases
IgA	15%	Mucosal immunity	Recurrent respiratory and GI infections (IgA deficiency)
IgM	10%	Primary response, complement activation	Acute infections
IgE	<0.1%	Allergic reactions, parasitic defence	Allergic disorders, parasitic infections
IgD	~1%	B cell activation	Limited clinical use

Complement System

Definition

The complement system is a group of plasma proteins that enhance the ability of antibodies and phagocytic cells to clear pathogens. It plays a critical role in both innate and adaptive immunity.

Pathways of Activation

1. **Classical Pathway**:
   - Triggered by antigen-antibody complexes (IgG or IgM).
   - Involves C1, C2, and C4 components.
2. **Alternative Pathway**:
   - Activated directly by pathogen surfaces.
   - Involves C3, factor B, factor D, and properdin.
3. **Lectin Pathway**:
   - Triggered by mannose-binding lectin binding to microbial carbohydrates.

Functions of the Complement System

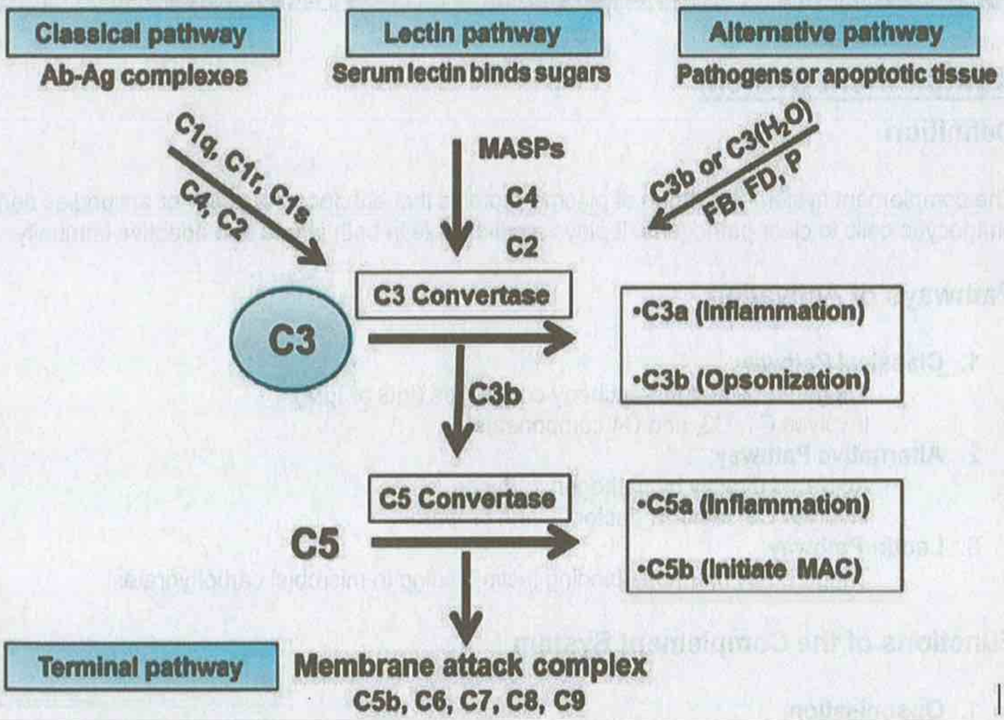
1. **Opsonisation**:
   - C3b binds to pathogen surfaces, enhancing phagocytosis by macrophages and neutrophils.
2. **Chemotaxis**:
   - C3a and C5a recruit immune cells to the site of infection.
3. **Cell Lysis**:
   - Formation of the membrane attack complex (MAC, C5b-C9) leads to lysis of pathogens.
4. **Clearance of Immune Complexes**:
   - Prevents immune complex deposition in tissues, reducing inflammation.

Regulation

- Complement activity is tightly regulated by proteins such as C1 inhibitor (C1-INH), factor H, and decay-accelerating factor (DAF) to prevent host tissue damage.

Complement cascade

The complement cascade is a crucial part of innate immunity, consisting of three activation pathways: **classical** (triggered by antigen-antibody complexes), **alternative** (direct pathogen surface activation), and **lectin** (mannose-binding lectin recognition). These pathways converge to activate **C3**, leading to opsonisation (C3b), inflammation (C3a, C5a), and the formation of the membrane attack complex (C5b-C9), which lyses pathogens.



The three pathways of complement activation are shown.

- Although each is triggered independently, they merge at the step of C3 activation.
- The classical pathway is initiated by the binding of antibody to antigen and the lectin pathway by the binding of lectin to a sugar molecule.
- The alternative pathway turns over continuously and is further amplified in the presence of pathogens or injured tissue.
- Activation of the complement system leads to inflammation (release of anaphylatoxins C3a and C5a), opsonization (the coating of targets with C3b and/or C4b), and formation of the membrane attack complex (MAC).

Complement Deficiencies

1. **C1q, C2, C4 Deficiency**:
   - Increased risk of autoimmune diseases (e.g., systemic lupus erythematosus).
2. **C5-C9 Deficiency**:
   - Recurrent infections with Neisseria species due to defective MAC formation.
3. **C1-INH Deficiency**:
   - Causes hereditary angioedema, characterised by episodes of swelling without urticaria.

Complement System Overview

Pathway	Trigger	Key Components	Outcome
Classical	Antigen-antibody complexes	C1, C2, C4	Opsonisation, cell lysis
Alternative	Pathogen surfaces	C3, factor B, factor D	Amplification of immune response
Lectin	Mannose-binding lectin	C2, C4, mannose-binding lectin	Opsonisation, pathogen clearance

Key Points

1. The complement system amplifies immune responses via three activation pathways: classical, alternative, and lectin.
2. **Complement functions** include opsonisation, chemotaxis, and cell lysis through the MAC.
3. **C3 is central to all complement activation pathways.**
4. Complement deficiencies result in susceptibility to infections or autoimmune diseases.

Autoimmune Diseases and Autoantibodies

Definition

Autoimmune diseases occur when the immune system loses self-tolerance and mounts an attack against the body's own tissues. This leads to chronic inflammation, tissue damage, and organ dysfunction.

Pathogenesis

1. **Loss of Self-Tolerance**:
   - Failure of central tolerance in the thymus or bone marrow.
   - Peripheral tolerance mechanisms (e.g., regulatory T cells) are also impaired.
2. **Genetic Predisposition**:
   - Strong associations with certain HLA types (e.g., HLA-DR3/DR4 in type 1 diabetes).
3. **Environmental Triggers**:
   - Infections (molecular mimicry, e.g., rheumatic fever).
   - Drugs (e.g., hydralazine-induced lupus).
4. **Epitope Spreading**:
   - Tissue damage exposes new antigens, perpetuating the autoimmune response.

Common Autoimmune Diseases and Their Autoantibodies

Disease	Key Autoantibodies	HLA Association	Clinical Features
Systemic lupus erythematosus (SLE)	ANA, anti-dsDNA, anti-Smith	HLA-DR2, HLA-DR3	Malar rash, arthritis, nephritis
Rheumatoid arthritis (RA)	Rheumatoid factor (RF), anti-CCP	HLA-DR4	Symmetrical polyarthritis
Type 1 diabetes mellitus (T1DM)	Anti-GAD, islet cell antibodies	HLA-DR3, HLA-DR4	Hyperglycaemia, ketoacidosis
Coeliac disease	Anti-tTG, anti-gliadin, anti-endomysial	HLA-DQ2, HLA-DQ8	Diarrhoea, malabsorption
Hashimoto's thyroiditis	Anti-TPO, anti-thyroglobulin	HLA-DR3, HLA-DR5	Hypothyroidism, goitre
Graves' disease	TSH receptor antibodies	HLA-DR3, HLA-B8	Hyperthyroidism, exophthalmos
Goodpasture's syndrome	Anti-GBM	None specified	Pulmonary haemorrhage, glomerulonephritis

Diagnostic Tools

1. **Indirect Immunofluorescence**:
   - Used for ANA testing in SLE.
2. **Enzyme-Linked Immunosorbent Assay (ELISA)**:
   - Quantifies specific autoantibodies (e.g., anti-dsDNA, anti-CCP).
3. **Tissue Biopsies**:
   - Used to confirm autoimmune damage (e.g., kidney biopsy in lupus nephritis).

Treatment Principles

1. **Immunosuppressive Therapy**:
   - Corticosteroids: Reduce inflammation.
   - Disease-modifying antirheumatic drugs (DMARDs): Methotrexate in RA.
   - Biologics: TNF-\u03b1 inhibitors (e.g., infliximab) for RA and SLE.
2. **Symptom Management**:
   - Hormonal replacement (e.g., thyroxine in Hashimoto's).
   - Organ-specific interventions (e.g., insulin in T1DM).

Key Points

1. Autoimmune diseases result from a loss of self-tolerance, with genetic and environmental contributions.
2. Key autoantibodies help diagnose and differentiate autoimmune diseases.
3. HLA types are strongly associated with specific autoimmune disorders.
4. Treatment often involves immunosuppressants and biologics to control disease activity.

Primary immunodeficiency

Disorders may be classified according to which component of the immune system they affect.

Neutrophil disorders

Disorder	Underlying defect	Notes
Chronic granulomatous disease	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	**Caused by** a failure of intracellular killing (no respiratory burst). Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. *Staphylococcus aureus* and fungi (e.g. *Aspergillus*) Negative nitroblue-tetrazolium test Screening is by the nitroblue tetrazolium (NBT) test Abnormal dihydrorhodamine flow cytometry test
Chediak-Higashi syndrome	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets
Leukocyte adhesion deficiency	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection

B-cell disorders

Disorder	Underlying defect	Notes
Common variable immunodeficiency **CVID**	Many varying causes	Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphona
Bruton's (x-linked) congenital agammaglobulinaemia	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen Absence of B-cells with reduce immunoglogulins of all classes
Selective immunoglobulin A deficiency	Maturation defect in B cells	• **Most common primary antibody deficiency**.

Disorder	Underlying defect	Notes
		• Recurrent sinus and respiratory infections • Associated with coeliac disease and **may cause false negative coeliac antibody screen**

T-cell disorders

Disorder	Underlying defect	Notes
DiGeorge syndrome	22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate

Combined B- and T-cell disorders

Combined B- and T-cell disorders: SCID WAS ataxic (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia)

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Most common **(X-linked)** due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. **Other causes include adenosine deaminase deficiency**	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles **Stem cell transplantation may be successful**
Ataxia telangiectasia	Defect in DNA repair enzymes	• Autosomal recessive. • Features include: 1. cerebellar ataxia, 2. telangiectasia (spider angiomas), 3. recurrent chest infections 4. and 10% risk of developing malignancy, lymphoma or leukaemia

Disorder	Underlying defect	Notes
Wiskott-Aldrich syndrome	Defect in WAS gene	X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy

Selective IgA deficiency

The history of mucosal infections (sinus and gastrointestinal) and the family history of immune cytopenia and coeliac disease are suggestive of selective IgA deficiency.

Definition

- **Most common primary immunodeficiency** that is characterized by a near or total absence of serum and secretory IgA

Features

- **Often asymptomatic**
- **Recurrent infections**
  - ⇨ May manifest with sinusitis or respiratory infections (S. pneumoniae, H. influenzae)
  - ⇨ Chronic diarrhea, partially due to elevated susceptibility to parasitic infection (e.g. by Giardia lamblia)
- **Associated with autoimmune diseases** (e.g., gluten-sensitive enteropathy, inflammatory bowel disease, immune thrombocytopenia) and atopy
  - ⇨ **10-fold increased risk of coeliac disease**
  - ⇨ Pernicious anaemia and hence gastric carcinoma
  - ⇨ **↑ Adverse reactions to blood products**
    - Patients with selective IgA deficiency should be tested for the presence of anti-IgA antibodies prior to transfusion with blood products.
- **Anaphylactic reaction to products containing IgA** (e.g., intravenous immunoglobulin)
- **Associated with IgG2 deficiency**
  - ⇨ **They are more likely than the general population to have an IgG2 deficiency, leading to recurrent bacterial infections**
  - ⇨ **The possibility of IgG2 deficiency should always be investigated in IgA-deficient individuals with a history of recurrent bacterial infections, but Staphylococcus aureus is the exception**

The Six A's of selective IgA deficiency: Asymptomatic, Airway infections, Anaphylaxis to IgA-containing products, Autoimmune diseases, Atopy

Diagnosis

- **low serum IgA level, with normal IgG and IgM levels**
- False-positive pregnancy tests

Treatment

- No specific treatment
- Prophylactic antibiotics
- Intravenous infusion of IgA is not recommended because of the risk of anaphylactic reactions (caused by the production of anti-IgA antibodies).

> **To prevent transfusion reactions, IgA-deficient patients must be given washed blood products without IgA or obtain blood from an IgA-deficient donor.**

IgG subclass deficiency

Definition

- IgG subclass deficiency is characterised by a lack or reduction of one or more IgG subclasses (IgG1, IgG2, IgG3, IgG4), while **total IgG levels may remain normal.** It can lead to increased susceptibility to infections.

IgG Subclasses and Their Roles

- **IgG1**: **Most abundant**; important for antibody-dependent cellular cytotoxicity and opsonisation. **Deficiency almost always presents as hypogammaglobulinemia.**
- **IgG2**: Targets polysaccharide antigens, crucial for immunity against encapsulated bacteria. Deficiency → Infections with *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis* → **multiple presentations with otitis media and respiratory tract infections.**
- **IgG3**: Potent in complement activation; responds to protein antigens. Deficiency More common in adults → Infections with Moraxella catarrhalis and S. pyogenes are typical → frequent chronic sinusitis.
- **IgG4**: **Least abundant;** involved in chronic antigen exposure and immune tolerance. Deficiency may or may not be associated with symptomatic sinopulmonary infections.

Clinical Features

- Recurrent respiratory infections (sinusitis, otitis media, bronchitis).
- Poor response to polysaccharide vaccines (e.g., pneumococcal vaccine).
- May occur as an isolated deficiency or alongside other immunodeficiencies, such as common variable immunodeficiency (CVID).

Diagnosis

- **Measurement of IgG Subclass Levels**: Blood tests for individual IgG subclasses.
- **Functional Antibody Responses**: Assessment after vaccination to evaluate immune function.
- **Exclusion of Other Disorders**: Rule out conditions like CVID or secondary immunodeficiencies.

Treatment

1. **Preventative Measures**:
    - Vaccination, including conjugate vaccines for encapsulated bacteria.
    - Antibiotic prophylaxis in severe cases.
2. **Immunoglobulin Replacement Therapy (IVIG/SCIG)**:
    - Indicated for patients with recurrent severe infections and documented antibody deficiency.

Isolated IgD deficiency

- IgD are surface receptors of B lymphocytes
- No specific signs or symptoms
- **increased viral respiratory tract infections**,
    - ⇨ **IgE** deficiency leads to both **viral and parasitic infections**
- IgA, IgG and IgM levels are entirely normal
- Isolated IgD deficiency has been identified amongst people of Basque origin, hence the link to northern Spain
- Not require any specific treatment

Common variable immunodeficiency (CVID)

Definition

- primary immunodeficiency with low serum levels of all immunoglobulins despite phenotypically normal B cells

Epidemiology

- **The most common clinically significant primary immunodeficiency** is CVID.
    - ⇨ IgA deficiency is more common, but most are asymptomatic.
- Sex: ♀ = ♂
- Onset: present later than other B cell defects (usually 20–35 years of age)

Pathophysiology

- Most cases are sporadic with no known family history **(No clear pattern of inheritance)**
- B cells are phenotypically normal but are unable to differentiate into Ig-producing cells,(**B-cell dysfunction**) resulting in low immunoglobulins of all classes.

Features

- Recurrent pyogenic respiratory infections, e.g., sinopulmonary infections (in rare cases, enteroviral meningitis)
- Associated with a high risk of **lymphoma**, gastric cancer, **bronchiectasis**, and autoimmune disorders (e.g., rheumatoid arthritis, autoimmune hemolytic anemia, immune thrombocytopenia, vitiligo)

Investigations

- Quantitative immunoglobulin levels: **low levels of IgG, IgA, and IgM**
- Decreased number of plasma cells
- Flow cytometry shows subsets of **normal B and T cells**
- Poor response to immunizations

Treatment

- **Intravenous immunoglobulin** (IVIG) replacement therapy (**first line**), **the best option to prevent recurrent chest infections.**
- Prophylactic antibiotics

> ➲ **CVID →B-cell Cannot differentiate into plasma cells → low immunoglobulins but normal or decreased B cells.**
> ➲ **Bruton's → Pre-B lymphocytes are increased because there's a maturation defect.**

> **MRCP-part-1-May-2018**
> H/O **recurrent Giardia lamblia diarrhea and multiple upper respiratory infections** since birth. serum analysis reveals **normal levels of mature B lymphocytes**. What other finding on serum analysis predisposes the patient to recurrent diarrheal infections?
> ➲ **Deficiency in IgA**
> - The patient has **common variable immunodeficiency disorder (CVID)**
> - IgA prevent the binding of pathogens to the epithelial cells; thus, preventing protozoa like Giardia lamblia from causing inflammation. Its absence, therefore, leads to the increased likelihood of repeat infection of the GI mucosa

Bruton's agammaglobulinemia (X-linked agammaglobulinemia)

> **Live vaccines (e.g., MMR) are contraindicated in patients with Bruton agammaglobulinemia.**

Pathophysiology

- **X-linked recessive** disease caused by a mutations in the gene coding for **Bruton tyrosine kinase** (BTK) leads to **complete deficiency of B lymphocytes**
- The most common genetic event is a **missense mutation** (substitution in one amino acid in a protein).

Epidemiology: occurs mainly in boys

Features

- Symptoms develop between 3 and 6 months of age when maternal IgG levels in fetal serum start to decrease.
- Hypoplasia of lymphoid tissue (e.g., tonsils, lymph nodes)
- Recurrent, severe, pyogenic infections (e.g., pneumonia, otitis media), especially with encapsulated bacteria (S. pneumoniae, N. meningitidis, and H. influenzae)
- Hepatitis virus and enterovirus (e.g., Coxsackie virus) infections

Diagnosis

- Flow cytometry
  - ⇨ Absent or low levels of B cells (marked by CD19, CD20, and CD21)
  - ⇨ Normal or high T cells
- Low immunoglobulins of all classes
- Absent lymphoid tissue, i.e., no germinal centers and primary follicles

Treatment

- IV immunoglobulins
- Prophylactic antibiotics

Severe combined immunodeficiency disease (SCID)

SCID is due to either a deficiency in IL-2R gamma chain (most common, X-linked) or deficiency in adenosine deaminase (autosomal recessive)

Overview

- **Numerous genetic mutations → Combined B- and T-cell disorder →** immunodeficiency
- **X-linked recessive** mutations → defective IL-2R gamma chain receptor linked to JAK3 (**most common SCID mutation)**
- Autosomal recessive → Adenosine deaminase deficiency (it aid in breakdown of deoxyadenosine, which is a breakdown product of DNA) → Accumulation of toxic metabolites (**deoxyadenosine** and dATP) (Deoxyadenosine is toxic to lymphocytes, thus accumulation of this leads to apoptosis of lymphocytes)

Features (usually manifests in the first year of life)

- Recurrent infections
- Diarrhea
- Dermatitis
- Failure to thrive
- Lymph nodes and tonsils may be absent

Diagnosis

- Flow cytometry: absent T cells , abnormal function of B-cells
- CXR: absent thymic shadow
- Lymph node biopsy: absent germinal centers
- ↓ Lymphocyte count (< 3000/μL)

Treatment

- Bone marrow transplantation (the best initial curative treatment)

Prognosis

- Without intervention, SCID usually results in severe infection and death in children by age 2 years.

DiGeorge syndrome

DiGeorge syndrome - a T-cell disorder

Definition

- A syndrome characterized by defective development of the third and fourth pharyngeal pouches leading to hypoplastic thymus and parathyroids

Pathophysiology

- **Autosomal dominant**; microdeletion at **chromosome 22** → Abnormal development of the third and fourth pharyngeal pouches → thymic aplasia and defective parathyroid → **T-cell deficiency and dysfunction** → primary immunodeficiency
  - ⇨ **The thymus arises from the 3rd pharyngeal pouch,**
  - ⇨ **the parathyroid glands receive contribution from both 3rd and 4th pouches.**
- It is an example of a microdeletion syndrome.

Features

- Thymus aplasia/hypoplasia → Recurrent infections (viral/fungal/PCP pneumonia) due to T-cell deficiency
- Parathyroid gland hypoplasia → hypocalcaemic tetany
- **Cardiac anomalies:** (e.g., tetralogy of Fallot, VSD, ASD)
- **Facial abnormalities:**
  - ⇨ Cleft palate
  - ⇨ Micrognathia (small lower jaw) and/or retrognathia
  - ⇨ Dysplastic ears
  - ⇨ High and broad nasal bridge

Investigations

- **Chest X-ray shows absence of the thymic shadow.**
- **Low levels of serum calcium** (Ca^{2+}) **and parathormone** (PTH)
- ↓ Absolute T-lymphocyte count
- Delayed hypersensitivity skin testing
- Fluorescence in situ hybridization (FISH) → Detection of 22q11.2 deletion

> **MRCP-part-1- May 2019 exam: In a patient having DiGeorge syndrome, which infection is he most at risk from, secondary to his immune system dysfunction?** ***Cryptococcus neoformans*** (T-cell dysfunction → ↑↑ risk from recurrent viral and fungal infections)

Wiskott-Aldrich syndrome (WAS)

> **Wiskott-Aldrich syndrome: Classic tetrad of:**
> 1. **Purpura (bleeding diathesis)**
> 2. **Eczema (high risk of atopic disorders)**
> 3. **Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)**
> 4. **↑ Risk of autoimmune diseases and hematological malignancies**

Definition

- Wiskott-Aldrich syndrome (WAS) is defined as an X-linked hereditary disorder associated with adaptive and innate immunodeficiency, micro-thrombocytopenia, eczema, and an increased risk of autoimmune disorders and malignancy.

Pathophysiology

- "Loss-of-function" mutation in **WASP gene** (**X-linked recessive inheritance**) → combined **B- and T-cell** dysfunction and thrombocytopenia

Epidemiology: occurs primarily in males

Features

- **Classic tetrad**
  1. Purpura (bleeding diathesis)
  2. Eczema (high risk of atopic disorders)
  3. Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)
  4. **Increased risk of autoimmune diseases and hematological malignancies** (e.g., lymphoma, leukemia)

Investigations

- Thrombocytopenia with small platelets
- Low IgM and IgG levels
- ↑ IgE and IgA
- Genetic analysis (confirmatory test): mutated WASp gene

Prognosis

- The disease has **variable penetrance**, which means that life expectancy can range from 6 - 30 years.

Complement deficiencies

- **C3 deficiency is associated with recurrent bacterial infections,**
- **C5 deficiency is more characteristically associated with disseminated meningococcal infection**

- Deficiencies of the **classical** complement pathway such as **C1 and C4** deficiencies are strongly associated with the development of **systemic lupus erythematosus**;
- deficiencies of the **alternative** pathway, such as **C3 and C5–9**, are associated with increased risk of **recurrent pyogenic infections**.

Overview

- Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body.
- Complement proteins are involved in chemotaxis, cell lysis and opsonisation.
- Most of complement deficiencies are inherited in autosomal recessive fashion; the exception being properdin deficiency, which is usually described as having an X-linked inheritance pattern.

C1 inhibitor (C1-INH) protein deficiency

- causes hereditary angioedema
- C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura, vasculitidies
- mechanism
  - ⇨ complement activity is associated with clearance of circulating immune complexes
  - ⇨ If immune complexes are not cleared, they undergo → tissue deposition where an inflammatory process is triggered, leading to SLE

C3 deficiency

- causes recurrent bacterial infections
- Deficiencies of **C3** is more commonly associated with **haemolytic uraemic syndrome**

C5 deficiency

- predisposes to Leiner disease
- recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency

- encodes the membrane attack complex (MAC)
- particularly prone to ***Neisseria meningitidis*** infection
- **Absent classical and alternate pathway activity**

Membrane attack complex (MAC)

- Formed by C5b, C6, C7, C8, and multiple copies of C9 complement proteins on pathogen cell membranes
- Function → lyses pathogens
- Inhibited by CD59
  - ⇨ This exists on body cells to protect them from MAC.
  - ⇨ paroxysmal nocturnal haemoglobinuria, results in red cells that lack CD59. These red cells can, therefore, be lysed by MAC.

Decay-accelerating factor (DAF) deficiency is associated with → Paroxysmal nocturnal haemoglobinuria (PNH).

Diagnosis

- **CH50 assay screening test**

MRCPI-part-1-jan-2017: Post splenectomy what type of immunodeficiency is occurs?

➲ Humoral

- Post splenectomy there is increased susceptibility to H. Influenzae, N. Meningitidis and Strep pneumonia which are encapsulated organisms **due to the loss of splenic macrophages which are part of the humoral response.**

> **MRCPUK-pat-1-May 2019 exam: A 23-year-old man is admitted with sepsis. Blood cultures are reported as *Neisseria gonorrhoeae*. Which complement protein is the patient most likely to deficient in?**
> - C5-9

Hereditary angioedema

> Hereditary angioedema - C1-INH deficiency
>
> Hereditary angioedema - C4 is the best screening test inbetween attacks

Overview

- Hereditary angioedema is an **autosomal dominant** condition associated with **low plasma levels of the C1 inhibitor (C1-INH) protein**.
- C1-INH is a multifunctional serine protease inhibitor

Pathophysiology

- Deficiency of C1 esterase inhibitor leads to persistent activation of the classical complement pathway and C4 levels are frequently low secondary to activation and consumption.
  - ⇨ ↓C1 inhibitor allow C1 to act on C4 and C2
- Mechanism of attacks : uncontrolled release of **bradykinin** resulting in oedema of tissues.

Investigation

- C1-INH level is low during an attack
- Low C2 and C4 levels are seen, even between attacks.
- **Serum C4 is the most reliable and widely used screening tool**
- Angioedema does not readily cause a rise in mast cell tryptase.

Features

- Painless, non-pruritic swelling of subcutaneous/submucosal tissues
  - ⇨ urticaria is not usually a feature
  - ⇨ attacks may be proceeded by painful macular rash
- May affect upper airways, skin, genital or abdominal organs (can occasionally present as abdominal pain and vomiting due to visceral oedema)
- Triggers include stress, infection and menstruation

Management

- **Acute**: IV C1-inhibitor concentrate (1000-1500 units given intravenously over 20-30 min),
  - ⇨ fresh frozen plasma (FFP) if this is not available
- **Prophylaxis**:
  - ⇨ Anabolic steroid, synthetic androgen: Danazol may help
  - ⇨ Aminocaproic acid

Complication

- **If treatment fails to normalise the C4 levels and they remain persistently low, these patients are at an increased risk of developing SLE.**

Other Causes of angioedema

- **Bradykinin-mediated angioedema**
  - ⇨ Hereditary angioedema (inherited C1 inhibitor deficiency)
  - ⇨ Acquired angioedema (acquired C1 inhibitor deficiency)
    - Often associated with lymphoproliferative diseases and B-cell malignancies
  - ⇨ ACE inhibitor-induced (rarely ARB-induced): impaired bradykinin breakdown
    - Can occur within days to 2 years after starting ACE inhibitor
- **Histamine-mediated angioedema (mast cell-mediated angioedema)**
  - ⇨ Usually coexist with urticaria
  - ⇨ Salicylate- and/or aspirin-associated angioedema
  - ⇨ **Moxonidine is a centrally acting antihypertensive and is associated with angioedema**
- **Idiopathic angioedema:** Possible triggers: cold, heat, stress, and exercise

Hypersensitivity

The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types:

Type	Mechanism	Examples
Type I - Anaphylactic	Antigen reacts with **IgE** bound to mast cells (**IgE-mediated**)	• Anaphylaxis • Atopy (e.g. asthma, eczema and hayfever) **Diagnosed by plasma tryptase** (protease released from mast cell).
Type II - Cell bound	IgG or IgM binds to antigen on cell surface (**antibody-mediated**)	• Autoimmune haemolytic anaemia • ITP • Goodpasture's syndrome • Pernicious anaemia • Acute haemolytic transfusion reactions • Rheumatic fever • Pemphigus vulgaris / bullous pemphigoid
Type III - Immune complex	Free antigen and antibody (IgG, IgA) combine (**Immune complex deposition**)	• Serum sickness • Systemic lupus erythematosus • Post-streptococcal glomerulonephritis • Extrinsic allergic alveolitis (especially **acute phase**)

Type	Mechanism	Examples
Type IV - Delayed hypersensitivity	T-cell mediated (cell-mediated)	• Tuberculosis / tuberculin skin reaction • Graft versus host disease • Allergic contact dermatitis • Scabies • Extrinsic allergic alveolitis (especially **chronic phase**) • Multiple sclerosis • Guillain-Barre syndrome

In recent times a further category has been added:

Type	Mechanism	Examples
Type V	Antibodies that recognise and bind to the cell surface receptors. This either stimulating them or blocking ligand binding	• **GraVes'** disease • Myasthenia **graVis**

What is the hallmark signs of mast cell degranulation?

- **Classical wheal and flare**

Anaphylaxis

Anaphylaxis = type I hypersensitivity reaction

Anaphylaxis - serum tryptase levels rise following an acute episode

Definition

- a severe type 1 hypersensitivity reaction that can cause life-threatening and multisystem effects due to IgE-mediated mast cell activation

Pathophysiology

- **Immunoglobulin E is the most common immunoglobulin involved in the pathogenesis of anaphylaxis.**
- Anaphylaxis (type I hypersensitivity reaction) or anaphylactoid reactions → degranulation of **mast cells** → massive histamine release → systemic vasodilation → increased capillary leakage → anaphylactic shock
- **Mediators involved in the development of anaphylaxis** include: Tryptase, histamine, leukotrienes, prostaglandins, **IL4, IL13**, Heparin and platelet aggregating factor, which are generated by mast cell degranulation.
- **Triggers for anaphylactic reactions:** heat, cold, sexual activity, **exercise**

Causes

1. **Anaphylaxis (IgE mediated):**
   - ⇨ Food (e.g. Nuts) - the most common cause in children
   - ⇨ Drugs
     - The most common IgE-mediated triggers are drugs, typically penicillin or other beta-lactam antibiotics.
     - Neuromuscular blocking agents (eg **vecuronium) are responsible for 60-70% of allergic reactions related to anaesthesia.**
   - ⇨ **Latex**
   - ⇨ Venom (e.g. Wasp sting)
2. **Anaphylactoid (non-IgE mediated).**
   - ⇨ The reactions that produce the same **clinical picture** as anaphylaxis **but are not IgE mediated**.'
   - ⇨ plasma proteins or compounds, which act directly on the mast cell membrane, such as
     - Vancomycin
     - Quinolone antibiotics
     - Aspirin or other non-steroidal anti-inflammatory drugs
     - Opiates
     - Colloid plasma expanders
     - Radiographic contrast media

Anaphylaxis following a blood transfusion can be due to immunoglobulin A deficiency.

Anaphylaxis VS Anaphylactoid

Is it anaphylactic OR anaphylactoid reaction?

	Anaphylactic (IgE-mediated anaphylactic reactions)	Anaphylactoid (Non-IgE-mediated anaphylactic reactions)
Is sensitization required?	Yes	**No**
Can reaction occur in first exposure?	**No**	Yes
How much exposure is needed to elicit reaction?	very little (dose independent)	usually more than for anaphylaxis
Is reaction predicted by skin allergy test?	Yes	**No**

Which feature is the most important predictor of anaphylaxis in asthmatic patient with peanut allergy?

➲ **Poorly controlled asthma**

- Poorly controlled asthma is an important risk factor for fatal anaphylaxis in this situation.
- Patients such as this should have their asthma well controlled and have ready access to, and knowledge of how to use, self-injectable adrenaline.

Features (Usually takes 15-30 minutes from the time of exposure to the antigen)

- **Skin or mucous membranes:** Flushing, erythema, pruritus, Swelling of the eyelids, angioedema
- **Respiratory:** hoarseness, Chest tightness, Dyspnea (due to bronchospasm or laryngeal edema), tachypnea, Stridor, wheezing, Hypoxia, cyanosis
- **Gastrointestinal:** Nausea, vomiting (especially in food allergies), Abdominal pain, diarrhea
- **Cardiovascular:** Hypotension, Tachycardia

Investigations

- **Serum mast-cell tryptase: if elevated, supports the diagnosis of anaphylaxis**
  - ⇨ has a half-life of 2 h, peaking at 1 h after anaphylaxis onset and return to baseline by 6 hours.
  - ⇨ Both sensitivity and specificity to confirm diagnosis is 95%
  - ⇨ **Normal tryptase results do not exclude anaphylaxis**
- Complement C4 levels: can be low in hereditary angioedema
- Total serum IgE level is **non-specific and unhelpful.**

Management

- Airway assessment and management: Rapid sequence intubation (RSI) for airway compromise
- **Adrenaline**
  - ⇨ the most important drug in anaphylaxis and **should be given as soon as possible**.
  - ⇨ The dose for **adult and child > 12 years** : 500 micrograms (0.5ml **1 in 1,000**)
  - ⇨ The best site for IM injection is the anterolateral aspect of the middle third of the thigh.
  - ⇨ Adrenaline can be repeated every 5 minutes if necessary.
- Hydrocortisone 200 mg
- Chlorphenamine 10 mg
- IV fluids
  - ⇨ *Evidence from a large randomised controlled trial (RCT) suggests there is no difference between normal saline and* Hartmann's solution [also known as Ringer's lactate] *for resuscitation of critically ill patients*.
- Observation: It is recommended to observe patients after resolution of an anaphylactic episode for 24 hours **for possible second-phase reactivation.**

Management of Anaphylaxis

Step	Intervention	Details
Initial	Adrenaline (IM)	0.5 mg, repeat every 5 minutes if needed
Supportive	Oxygen	High flow (10–15 L/min)
Fluids	IV crystalloids	1–2 L bolus for hypotension
Antihistamines	Chlorphenamine	10 mg IM or IV
Corticosteroids	Hydrocortisone	200 mg IV

Late-phase reaction

In IgE mediated reactions such as asthma or anaphylaxis what therapy inhibits the important late-phase reaction? steroids

- The late phase reaction is due to attraction of T cell, release of leukotrienes and prostaglandins often characterised by asthma
- prevented by the administration of steroids (**Hydrocortisone**).
- Approximately **30% of deaths related to anaphylaxis occur as a consequence of this late-phase reaction**

Epinephrine injections for anaphylaxis should always be given intramuscularly in a concentration of 1:1,000 (as opposed to the 1:10,000 solution used in cardiac arrest). Injecting the 1:1,000 solution into a vein can lead to cardiac arrhythmia/arrest.

Antihistamines and steroids should be administered in anaphylaxis only after the initial resuscitation measures (IM epinephrine, fluids and/or vasopressors) have been given.

A lack of response to epinephrine, antihistamines, and steroids should raise suspicion of differential diagnoses such as bradykinin-mediated angioedema, which requires its own specific treatment

Exercised induced anaphylaxis

Definition

- a rare disorder in which anaphylaxis occurs after physical activity.

Features

- usually **occur around 10 minutes after exercise** and follow a sequence of pruritus, widespread urticaria and then subsequently respiratory distress and vascular collapse.

Pathophysiology

- may be related to **endorphin release during exercise** → excessive histamine release from mast cells in susceptible individuals.

Associations

- Co-factors such as foods, alcohol, temperature, drugs (eg, aspirin and other nonsteroidal anti-inflammatory drugs), humidity, seasonal changes, and hormonal changes are important in the precipitation of attacks.
- most associated with wheat ingestion.
- The foods most commonly implicated in food-dependent exercise-induced anaphylaxis are wheat, shellfish, tomatoes, peanuts, and corn.
- The patients can usually eat the causative food without problems so long as they do not exercise afterwards.

Treatment
- managed in the same manner as anaphylaxis.
- usually resolves on stopping exercise
- Reducing physical activity to a lower level may diminish the frequency of attacks.
- **Patients should be instructed on the proper use of emergency injectable epinephrine** and have one available at all times.
- Patients should wear a medical alert bracelet with instructions on the use of epinephrine.

Anaphylactic reactions associated with anaesthesia

Risk factors
- Neuromuscular blocking drugs and latex appear to cause anaphylaxis more commonly in **female** patients
- Individuals with a **history of atopy, asthma or allergy to some** foods appear to be at **increased risk of latex allergy** **but not anaphylaxis to neuromuscular blocking drugs or antibiotics**
- Patients with **asthma** or taking **b-blocking drugs** may suffer a more severe reaction.

Causes
- **Neuromuscular blocking agents (NMBAs)**
  - ⇨ **Most common cause**
  - ⇨ **60% of cases of anaesthesia-related anaphylaxis are due to neuromuscular blocking agents.**
  - ⇨ 80% of NMBA reactions occur without prior exposure
  - ⇨ Quaternary ammonium ions (QAI) are proposed to be the allergenic epitopes in NMBAs.
  - ⇨ Common environmental chemicals such as toothpastes, washing detergents, shampoos, and **cough medicines** share these allergenic epitopes with the NMBAs, predisposed individual to become sensitised to QAIs and thus be at **risk of developing anaphylaxis to NMBAs during anaesthesia.**
  - ⇨ **succinylcholine** is the NMBA **most likely** to be associated with **allergic anaphylaxis** (carries the highest risk)
- **Latex**
  - ⇨ Latex hypersensitivity is the second most common cause of anaesthesia related anaphylaxis in many studies (up to 20% of cases). **But now decreased due to decline in the use of latex gloves.**
- **Antibiotics**
  - ⇨ Approximately 15% of anaesthesia-related anaphylactic episodes are due to **antibiotics**.
    - Skin testing is only approximately 60% predictive of clinical hypersensitivity. Penicillins and
    - cephalosporins which share the b-lactam ring are responsible for approximately 70% of antibiotic-induced anaphylaxis.
    - There is a higher rate of antibiotic allergy in smokers
- **Anaesthetic induction agents**
  - ⇨ Anaphylaxis to **propofol** is **very uncommon**
  - ⇨ Anaphylaxis to thiopental has become extremely uncommon, probably reflecting the decline in its use.

- **Antiseptics and disinfectants**
  - ⇨ Reactions to **chlorhexidine** have come into greater prominence in recent years.
  - ⇨ Anaphylaxis has occurred when chlorhexidine was used as an antiseptic for urological and gynaecological procedures as well as insertion of central venous and epidural catheters.
  - ⇨ Allowing chlorhexidine to dry before beginning a procedure may reduce the risk of reaction.
  - ⇨ Anaphylaxis to other antiseptics is rare.

Diagnosis

- **Timings**
  - ⇨ Type I reactions typically occur within **seconds to minutes** after **i.v. exposure.**
  - ⇨ An insidious or delayed onset may occur (e.g. with latex, antibiotics, and colloids and a tourniquet may delay onset until after surgery).
- **History of atopy and asthma has a clear link with latex allergy.**

Allergy tests

Skin prick test	• **Most commonly used test as an easy to perform and inexpensive.** • **the first line for detection of allergen-specific IgE** • **Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle.** • **A large number of allergens can be tested in one session.** • **Normally includes a histamine (positive) and sterile water (negative) control.** • **A wheal will typically develop if a patient has an allergy.** • **Can be interpreted after 15 minutes** • **Useful for food allergies and also pollen. It is a reliable way of excluding IgE-mediated food allergies, although the positive predictive value is around 50% or less (the sensitivity of a negative skin prick test to foods is high)** • **It can induce anaphylaxis, and must therefore be done in an environment where resuscitation facilities are available.**
Radioallergosorbent test (RAST)	• Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein. • Results are given in grades from 0 (negative) to 6 (strongly positive) • Useful for food allergies, inhaled allergens (e.g. Pollen) and wasp/bee venom • Blood tests may be **used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines**
Skin patch testing	• **Useful for contact dermatitis.** • Around 30-40 allergens are placed on the back. • Irritants may also be tested for. • The patches are **removed 48 hours later** with the results being read by a dermatologist after a further 48 hours

If a history of anaphylaxis is given it would not be appropriate to perform a skin prick test, thus Radioallergosorbent test (RAST) is the most appropriate first-line test to investigate the cause of the reaction

Reasons for a false negative RAST test

- Immediately following anaphylaxis / allergic reaction (transient drop in IgE)
- Waning of allergen-specific IgE with time following a reaction.
- Unstable allergens in the RAST substrates (especially food allergens)

Only IgE-mediated allergic reactions can be tested by skin prick testing

The wheal size resulting from the skin prick test is an excellent predictor of a positive food challenge to peanuts

Latex allergy

Definition

- A type I or type IV hypersensitivity to latex-based products (e.g., exam gloves, condoms)

Epidemiology

- 8–12% of health care workers are affected
- NHS trusts in the UK have moved away from the routine use of latex gloves precisely because of the risk of allergy. As a result, **latex allergy in hospital is now very rare in the UK.**
- Latex allergy is more common in children with myelomeningocele spina bifida.

Pathophysiology

- Sensitivity to latex may cause several problems:
  - ⇨ type I hypersensitivity (anaphylaxis)
    - ▪ **it is very unlikely that a latex allergy would explain an anaphylaxis during anaesthetic induction** (latex allergies typically used to commence when a surgeon began handling internal organs).
  - ⇨ type IV hypersensitivity (allergic contact dermatitis)
    - ▪ **Type 4** hypersensitivity is usually **due to accelerators or chemicals used in the manufacturing** process, whereas **type 1** hypersensitivity is due to the **latex proteins themselves**
  - ⇨ irritant contact dermatitis

Latex-fruit syndrome

- It is recognised that many people who are allergic to latex are also allergic to fruits, particularly **banana**, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry. **However, bananas are the most commonly associated with latex/rubber allergy**

Latex allergy can be associated with certain foods such as bananas, avocado, kiwi and melon.

MRCPUK part-1-May 2016 exam: A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed? Banana

Serum Sickness

Definition

- Serum sickness is a classic example of a **type III hypersensitivity reaction**, which usually develops as a complication of antitoxin or antivenom administration.

Aetiology

- Antivenom or antitoxin containing animal proteins
- Medications most frequently antibiotics (e.g., penicillin, amoxicillin, cefaclor, trimethoprim-sulfamethoxazole)
- Infections: Hepatitis B virus

Pathophysiology

- exposure to an antigen (e.g., antivenom, drug) → formation of antibodies → deposition of antibody-antigen complexes in tissue → activation of the complement cascade → tissue damage and systemic inflammation

Features

- Symptoms appear 1–2 weeks following initial exposure (because antibodies take several days to form), and usually resolve within a few weeks after discontinuation of the offending agent.
- Fever
- Rash (urticarial or purpuric)
- Arthralgias
- Lymphadenopathy

Subtypes and variants: serum sickness-like reaction

- much more common than actual serum sickness
- Aetiology: similar to that of serum sickness
- Infections (e.g., hepatitis B, rabies)
- Medications that can act as haptens (e.g., allopurinol, cephalosporins, penicillin).

Diagnostics: Urinalysis may show mild **proteinuria**.

Treatment: Stop the offending agent.

This Page Is Intentionally Left Blank

4th edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences

Biochemistry & metabolism

Updated

2025

Anion gap (AG)

Renal tubular acidosis causes a normal anion gap

- The anion gap allows for the differentiation of 2 groups of metabolic acidosis.
  1. **Metabolic acidosis with a high AG** is associated with the **addition of** endogenously or exogenously **generated acids**.
  2. **Metabolic acidosis with a normal AG** is associated with the **loss of HCO_3 or the failure to excrete H^+ from the body.**
- The anion gap is calculated by: (sodium + potassium) - (bicarbonate + chloride)
- A normal anion gap is **8-14 mmol/L**
- It is useful to consider in patients with a metabolic acidosis:
  - ⇨ **Causes of a normal anion gap or hyperchloraemic metabolic acidosis**
    - gastrointestinal bicarbonate loss: diarrhoea, uretero-sigmoidostomy, fistula
    - renal tubular acidosis
    - **drugs: e.g. acetazolamide**
    - ammonium chloride injection
    - Addison's disease
  - ⇨ **Causes of a raised anion gap metabolic acidosis**
    - lactate: shock, hypoxia
    - ketones: diabetic ketoacidosis, alcohol
    - urate: renal failure
    - acid poisoning: salicylates, methanol

Mnemonic for normal gap metabolic acidosis (HARDUP):	Mnemonic for high anion gap acidosis → MUDPILES
• **Hyperchloremia** • **Acetazolamide, Addison's disease** • **Renal tubular acidosis** • **Diarrhea, vomiting, ileostomies, fistulae** • **Ureteroenteric fistulae** • **Pancreatoduodenal fistulae**	• **Methanol** • **Uremia** • **Diabetic ketoacidosis** • **Paraldehyde** • **Infection** • **Lactic acidosis** • **Ethylene glycol** • **Salicylates**

mnemonic of high anion gap acidosis:
- DR. MAPLES: D-DKA; R-renal; M-methanol; A-alcoholic ketoacidosis; P-paraldehyde, phenformin; L-lactic (ie, CO, HCN); E-ethylene glycol; S-salicylates

Metabolic acidosis associated with bladder reconstruction (e.g: for carcinoma of the bladder).

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild.
- Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient.
- Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and **treat metabolic acidosis with intravenous fluids and bicarbonate**.

Metabolic alkalosis

Pathophysiology

- Metabolic alkalosis may be caused by a **loss of hydrogen ions** (H+) or a **gain of bicarbonate** (HCO3).
- It is due mainly to problems of the **kidney** or **gastrointestinal tract**
- The initial disturbance of metabolic alkalosis is an increased HCO_3^- concentration, followed by a compensatory response of increased Pco_2.
- All renal tubular defects result in metabolic alkalosis, except for Fanconi syndrome.

ABG picture

- pH : Elevated
- PCO2: Expected compensatory response: ↑
- HCO3: Elevated

Compensation mechanism

- Hypoventilation is an immediate compensatory response to metabolic alkalosis.
- ↑ Arterial and CSF pH (with ↑ HCO3-) → ↓ stimulation of the medullary chemoreceptors → ↓ respiratory rate and/or tidal volume (hypoventilation) → ↑ CO2 retention → ↑ PCO2

Causes

- Vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenos, nasogastric suction)
- Diuretics
- Liquorice, carbenoxolone
- Hypokalaemia
- Bulimia nervosa
- Primary hyperaldosteronism
  - ⇨ Liddle syndrome
  - ⇨ Con syndrome
- Cushing's syndrome
- Bartter's syndrome
- Gitelman syndrome
- Congenital adrenal hyperplasia

Mechanism of metabolic alkalosis

- **The main mechanisms of metabolic alkalosis in the setting of vomiting are increased H+ excretion in the distal tubule and increased bicarbonate reabsorption in the proximal tubule.**
    - ⇨ ECF depletion (vomiting, diuretics) → Na^+ and Cl- loss → activation of renin-angiotensin II-aldosterone (RAA) system → ↑ aldosterone → reabsorption of Na^+ in exchange for H+ in the distal convoluted tubule
- In hypokalaemia, K^+ shift from cells to ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality

A patient with liver cirrhosis develops metabolic alkalosis. What **is the most likely pathological mechanism?** → **Reduced urea synthesis**

A patient in the intensive care unit following liver transplant surgery has a metabolic alkalosis.
What is the most likely cause?

➲ **Diuretic-induced volume depletion**
- Cirrhosis → hypoalbuminaemia → low colloid osmotic pressure → Relative volume depletion → ↑aldosterone, (which is not adequately metabolised by an impaired liver).
- **Furosemide use in the post-operative period further exacerbates alkalosis driven by hyperaldosteronism .**

Aetiology of metabolic alkalosis

Mechanism	Causes
Chloride-responsive metabolic alkalosis (urine chloride < 25 mEq/L)	➲ Gastrointestinal losses: due to vomiting, nasogastric suction, or diarrhea ➲ Renal losses: due to loop or thiazide diuretics ➲ Cystic fibrosis
Chloride-resistant metabolic alkalosis (urine chloride > 40 mEq/L)	➲ Severe magnesium deficiency ➲ Extreme hypercalcemia, hypokalemia ➲ High alkali load (e.g., due to antacid use, alkalization therapy) ➲ Loop or thiazide diuretics ➲ Other (less common causes) ▪ Associated with low or normal blood pressure ☞ Bartter syndrome ☞ Gitelman syndrome ▪ Associated with high blood pressure ☞ Hyperaldosteronism ☞ Cushing syndrome ☞ Liddle syndrome ☞ Licorice ingestion ▪ Ingestions or drugs (Laxative abuse, ampicillin, penicillin) ▪ Recovery from starvation ▪ Hypoalbuminemia

Prognosis

- when the pH is greater than 7.65 → mortality rate is 80%

Treatment

- Chloride-responsive metabolic alkalosis
  - ⇨ Start isotonic saline to increase urinary bicarbonate excretion and correct extracellular volume loss
- Chloride-resistant metabolic alkalosis
  - ⇨ Consider bicarbonate excess as a potential cause and administer acetazolamide.
  - ⇨ Acetazolamide is a diuretic used to alkalinize the urine or treat metabolic alkalosis as it inhibits carbonic anhydrase.

Respiratory acidosis

Causes

Mechanism	Causes
Acute respiratory acidosis	➲ Acute lung disease (e.g., pneumonia , pulmonary edema) ➲ Acute exacerbation of chronic obstructive airway disease (e.g., COPD, asthma) ➲ CNS depression due to: ▪ Head trauma ▪ Postictal state ▪ Drug toxicity (e.g., from opiates, barbiturates, benzodiazepines) ▪ Central sleep apnea
Chronic respiratory acidosis	➲ Airway obstruction (e.g., COPD, asthma) ➲ Respiratory muscle weakness, e.g., due to: ▪ Myasthenia gravis ▪ ALS ▪ Guillain-Barré syndrome ▪ Poliomyelitis ▪ Multiple sclerosis ▪ Severe hypokalemia

Features

Signs and symptoms of respiratory acidosis		
Central nervous system	**Respiratory system**	**Cardiovascular system**
Cerebral vasodilation	Breathlessness	Flushing, bounding pulse
Increased intracranial pressure	Cyanosis	Cor pulmonale
Headache, confusion, agitation	Pulmonary hypertension	Systemic hypotension
Hallucinations, transient psychosis		Arrhythmias
Myoclonic jerks, flapping tremor, extensor plantars, depressed reflexes		Initially good cardiac output, then decreases
Papilloedema, constricted pupils		
Seizures, coma		

Mechanism

- Alveolar hypoventilation → CO2 retention

ABG picture

- pH : low
- PCO2: elevated
- HCO3: Expected compensatory response: ↑

Treatment

- Consider noninvasive or invasive mechanical ventilation.

Respiratory alkalosis

Mechanism

- ↑ Respiratory rate and/or tidal volume → alveolar hyperventilation → CO2 washout

Causes

- Anxiety leading to hyperventilation (Hyperventilation will result in carbon dioxide being 'blown off', causing an alkalosis.) → high PH, low PCO2, normal PO2.
  - ⇨ not associated with hypoxia.
- pulmonary embolism
- Acute severe asthma
  - ⇨ associated with hypoxia and normal or rising CO_2

- Drugs (salicylates, progesterone)
  - ⇨ salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis.
    - **Early stimulation of the respiratory centre** leads to a **respiratory alkalosis** whilst later the **direct acid effects of salicylates** (combined with acute renal failure) may lead to an **acidosis**.
- CNS disorders: stroke, subarachnoid haemorrhage, encephalitis
- High altitude
- **Pregnancy**
- Pain
- Excessive mechanical ventilation.
- Hepatic failure

ABG picture

- pH : elevated
- PCO2: low
- HCO3: Expected compensatory response: ↓

Differential diagnosis of respiratory alkalosis with type 1 respiratory failure (low pO_2 and low pCO_2.):

- Chronic venous thromboembolism (most likely).
- Pulmonary fibrosis (but basal crackles may be expected).

Calcium metabolism see endocrinology
Hypercalcaemia see endocrinology
Hypocalcaemia see endocrinology
Vitamin D see endocrinology

Hyperkalaemia

Definition

- Serum potassium level > 5 mEq/L

Regulation

- Plasma potassium levels are regulated by a number of factors including:
  - ⇨ Aldosterone
  - ⇨ acid-base balance
  - ⇨ insulin levels.
- Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule.

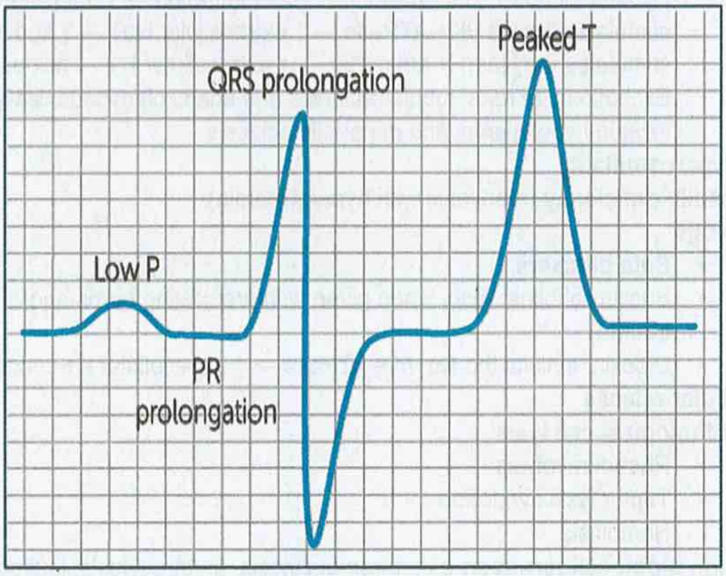
Causes

- **Potassium excess:** due to altered K+ metabolism or intake
  - ⇨ **Reduced excretion:** acute and chronic kidney disease
  - ⇨ **Endocrine causes:** hypocortisolism, hypoaldosteronism
  - ⇨ **Drugs:** potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers, NSAIDs, and trimethoprim-sulfamethoxazole
  - ⇨ **Type IV renal tubular acidosis**
  - ⇨ **Increased intake**
    - High potassium diet, e.g., bananas, oranges, kiwi fruit, avocado, spinach, tomatoes
    - K+ containing IV fluids
- **Extracellular shift**
  - ⇨ **Acidosis** → ↑ extracellular H+ → inhibition of the Na+/H+ antiporter → ↓ intracellular Na+ → ↓ sodium gradient inhibits the Na+/K+-ATPase → ↑ extracellular K+ concentration
    - Hyperkalemia → ↑ extracellular K+ concentration → ↑ potassium gradient stimulates the Na+/K+-ATPase → ↑ extracellular Na+ → ↑ sodium gradient stimulates the Na+/H+ antiporter → ↑ extracellular H+ → acidosis
    - Exceptions: In renal tubular acidosis and acetazolamide toxicity, findings include hypokalemia and metabolic acidosis.
  - ⇨ **Hyperosmolality**
  - ⇨ **Insulin deficiency** (manifests with hyperglycemia)
  - ⇨ **Drugs**
    - **Beta blockers**
    - Succinylcholine: (esp. when given with preexisting burns and/or muscle trauma) ,
    - Digoxin: inhibits the Na+/K+-ATPase → ↑ extracellular K+ concentration
- **Extracellular release**
  - ⇨ **Pathological cell lysis**
    - Rhabdomyolysis
    - Tumor lysis syndrome
    - Hemolysis
  - ⇨ **High blood cell turnover:** e.g., thrombocytosis, erythrocytosis, leukocytosis
  - ⇨ **Pseudohyperkalaemia:** resulting from iatrogenic red blood cell lysis
    - Blood drawn from the side of IV infusion or a central line without previous flushing
    - Prolonged use of a tourniquet
    - Fist clenching during blood withdrawal
    - Delayed sample analysis

When K+ shifts out of the cell, it's a BAD LOSS! – Beta blockers, Acidosis, Digoxin, Lysis, hyperOsmolality, high Sugar, Succinylcholine

Features

- May be asymptomatic
- Nausea, vomiting, diarrhea
- **Cardiac:** Arrhythmias (e.g., atrioventricular block, ventricular fibrillation)
- **Neuromuscular:** Muscle weakness, paralysis, paresthesia, ↓ Deep tendon reflexes
  - ⇨ Weakness and fatigue are the most common complaints
- **ECG changes**
  - ⇨ **Early changes** (typically seen at a serum potassium level of 5.5-6.5 mEq/L)
    - tall, peaked **T** waves
    - shortened **QT** interval
    - **ST**-segment depression.
  - ⇨ At a serum potassium level of 6.5-8.0 mEq/L, in addition to peaked T waves:
    - Decreased or disappearing **P** wave
    - Prolonged **PR** interval
    - Widening of the QRS
    - Amplified **R** wave



Treatments

Immediate treatment principles include:

1. Providing calcium salts to reduce the risk of arrhythmia (**'protect the heart'**);
2. Administering intravenous glucose and insulin (**'shift potassium into cells'**);
3. Reducing intake and increasing output of potassium (**'remove potassium from the body'**).

- Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors).
- **Mild chronic hyperkalaemia (eg: 5.6 mmol/l) is well tolerated and not a cause for concern.** If serum potassium rise to >6.0 mmol/l, standard practice would be to stop the ACEi and - if K >6.0 mmol/l were to persist - to advise a low potassium diet.
- **Stabilisation of the cardiac membrane**
  - ⇨ intravenous 10 ml 10% calcium gluconate (or calcium chloride)
  - ⇨ The effects of intravenous calcium occur within 1 to 3 minutes but last for only 30 to 60 minutes.
- **Short-term shift in potassium from extracellular to intracellular fluid compartment**
  - ⇨ Combined insulin/dextrose infusion:
    - ⇨ The most effective agent .
    - ⇨ In hyperglycaemic patients (serum glucose >15 mmol/L) insulin may be given without additional intravenous glucose.
    - ⇨ The dose: **10 units of soluble insulin**
  - ⇨ Nebulised salbutamol
    - Less effective than iv insulin and glucose (not recommended as monotherapy)
    - Patients prescribed beta blockers may be 'resistant' to the hypokalaemic effects of salbutamol.
- **Removal of potassium from the body**
  - ⇨ Calcium resonium (orally or enema)
  - ⇨ Loop diuretics
  - ⇨ Dialysis

May 2020 exam: H/O muscle weakness and lethargy. K+ = 6.3 mmol/l. What is the most appropriate initial treatment to lower the serum potassium level?
➔ **Insulin/dextrose infusion**

Pseudohyperkalaemia

High cell counts and high potassium: consider pseudohyperkalaemia

Causes

- Haemolysis during venepuncture
- Delay in the processing of the blood specimen
- Abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders or **essential thrombocytosis)**
- Familial causes

Management

- **Re-check a fresh sample at the hospital**
- Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium.

Hypokalaemia and acid-base balance

Hypokalaemia - U waves on ECG

Definition

- Serum potassium (K+) level < 3.5 mEq/L

Causes

Hypokalaemia with alkalosis

- Vomiting
- Diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis

- Diarrhoea
- Renal tubular acidosis
- Acetazolamide
- Partially treated diabetic ketoacidosis

Drug induced hypokalaemia

- Intracellular shifts of potassium with normal total body potassium, for example:
  - theophylline
  - β-agonists
  - caffeine
  - insulin

Other causes

- Loss of potassium stores, for example: chronic diuretic use
- **Magnesium deficiency** may also cause hypokalaemia. In such cases, **normalizing the potassium level may be difficult until the magnesium deficiency has been corrected**

In hyperthermia, as body temperature increases, what is <u>the earliest biochemical abnormality</u>?

- **Hypokalaemia**
  - As body temperature increases, such as occurs in hyperthermia due to heatstroke, the earliest abnormality is hypokalaemia.
  - This is thought to be due to increased K+ uptake by muscles as catecholamines stimulate the NA-K-ATPase transporter.
  - As the body temperature rises further, hyperkalaemia can develop with rhabdomyolysis and lactic acidosis.
  - The acid-base picture is of metabolic acidosis with compensatory respiratory alkalosis.

K+ acts like H+: Hypokalemia leads to alkalosis and vice versa

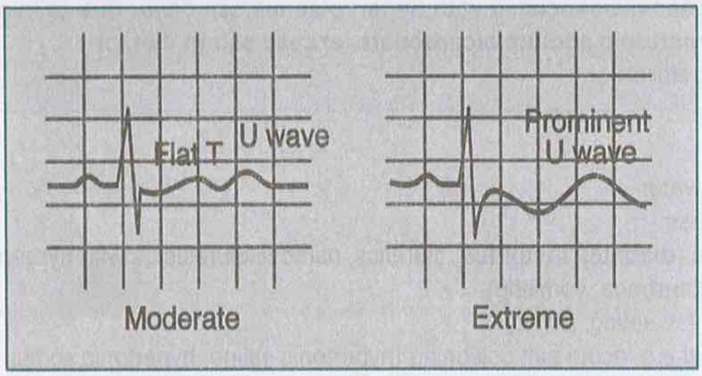
Hypomagnesemia can lead to refractory hypokalemia

Features

- Cardiovascular : cardiac arrhythmias
- Neuromuscular:
  - Muscle cramps and spasms
  - Muscle weakness
  - Decreased deep tendon reflexes
- Gastrointestinal: Constipation

ECG findings in hypokalemia

- Mild to moderate hypokalemia
  - ⇨ T-wave flattening or inversion
  - ⇨ ST depression
  - ⇨ Prolonged PR interval
- Moderate to severe hypokalemia
  - ⇨ QT prolongation
  - ⇨ Presence of U waves



Treatment

- If K >2.5 with no symptoms or ECG changes → oral potassium
- If K <2.5 with symptoms or ECG changes → IV potassium
- **In life-threatening cases → 1L IV 0.9% NaCL with 40 mmol/l KCl infused over four hours**
  - ⇨ Cardiac monitoring.
  - ⇨ Potassium should be given in NaCl.
  - ⇨ Concentration should not exceed 40 mmol/l
  - ⇨ No more than 10-20 mmol/hour should be given.

In patients with hypokalemia, avoid solutions containing dextrose, which can increase insulin secretion and worsen hypokalemia.

Daily maintenance requirements (NICE guidelines):

- Water → 1500-2500 ml/ day (25-30 ml/kg/day)
- Potassium, Sodium and Chloride → **1 mmol/kg/day**
  - ⇨ **Sodium → 70 mmol**
  - ⇨ **potassium → (40-80 mmol/day)** In the absence of kidney disease or hyperkalaemia (around 1 mmol/kg per day)

Estimation of total body potassium loss:

- **a drop in 1 mmol/L K^+ of serum potassium in approximately equivalent to a 200 mmol K^+ total body loss.**

Hypernatraemia

Hypernatraemia associated with hypovolaemia occurs due to a free water deficit. Common causes include reduced water intake (e.g. elderly), GI losses (e.g. vomiting and diarrhoea), skin losses (e.g. burns), and renal losses (e.g. osmotic diuresis)

Hypernatraemia associated with hypervolaemia can occur due to hypertonic saline, hypertonic sodium bicarbonate, excess salt in diet, or hyperaldosteronism

Causes

- Insufficient water
- free water loss:
  - ⇨ renal (**diabetes insipidus**, diuretics, osmotic diuresis as with hyperglycaemia),
  - ⇨ GI (diarrhoea, vomiting),
  - ⇨ skin (sweating, burns)
- Salt overload e.g. acute salt poisoning (hypertonic saline, hypertonic sodium bicarbonate), hyperaldosteronism

Treatment

- Treatment is aimed at the underlying cause.
- Hypernatraemia should be corrected with great caution.
- Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death.
- acute hypernatraemia can be corrected quickly but if chronic (>24hours) then it should be corrected at <0.5mmol/L/hr.
- Fluid resuscitation should involve oral water, 0.45% saline or 5% dextrose IV.

Hyponatraemia (serum sodium less than 135 mEq/L)

Mechanisms of causes

1. Water excess
2. Sodium depletion.
3. Pseudohyponatraemia:
   - ⇨ hyperlipidaemia (increase in serum volume)
   - ⇨ hyperproteinemia (e.g: myeloma)
   - ⇨ taking blood from a drip arm.

Cause of hyponatraemia

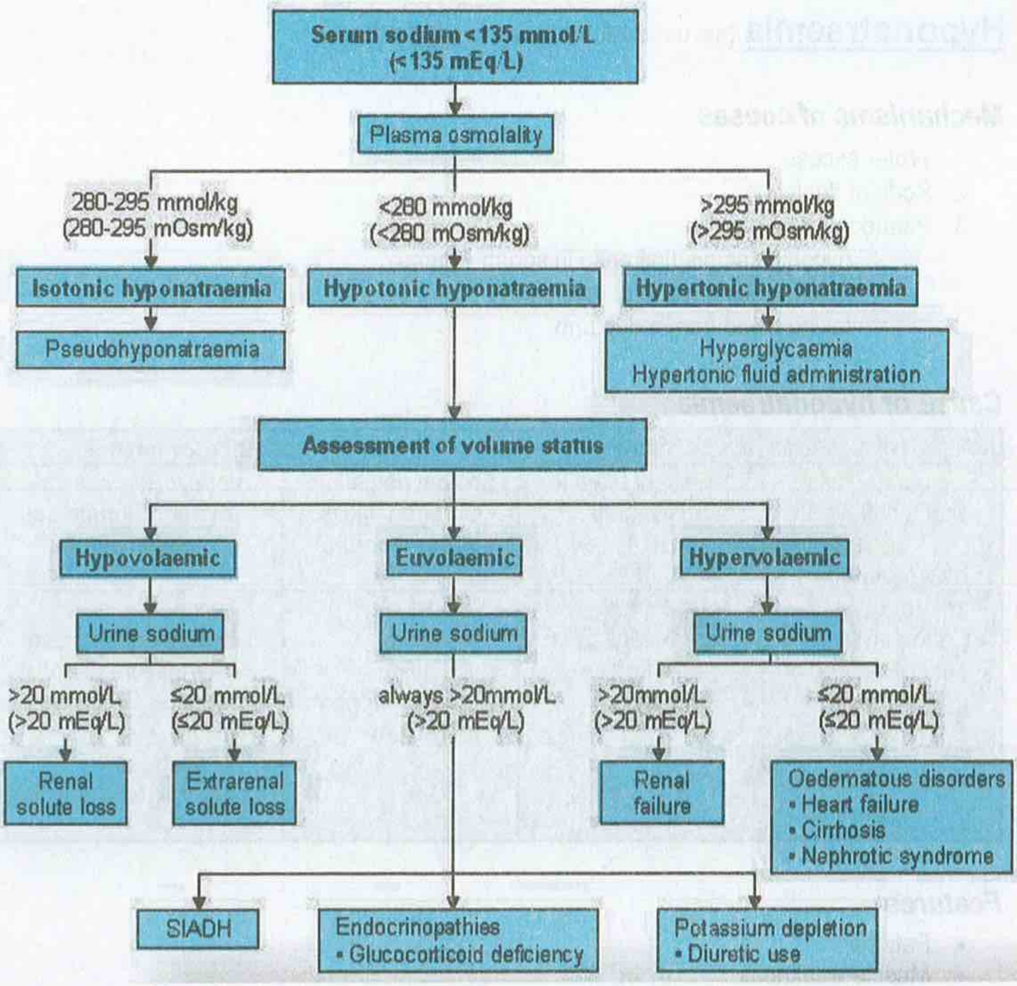
Urinary sodium > 20 mmol/l		Urinary sodium < 20 mmol/l	
Sodium depletion, renal loss (patient often hypovolaemic)	Patient often euvolaemic	Sodium depletion, extra-renal loss (hypovolaemic)	Water excess (patient often hypervolaemic and oedematous)
• diuretics • Addison's • diuretic stage of renal failure	• SIADH (urine osmolality > 500 mmol/kg) • hypothyroidism	• diarrhoea, vomiting, sweating • burns, adenoma of rectum	• secondary hyperaldosteronism: heart failure, cirrhosis • reduced GFR: renal failure • IV dextrose, psychogenic polydipsia

Features

- Fatigue
- Muscle weakness
- Gait disturbance
- Falls
- Disorientation
- Cerebral oedema
- Seizures

Investigations

- Urinary sodium and osmolarity levels aid making a diagnosis.
  - ⇨ urinary sodium
    - Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal.
    - may be misleading in the presence of renal impairment or diuretic therapy.



Management

- It is important with hyponatraemia to ascertain volume status as this will determine management.
- The management of each is as follows:
  - ⇨ **Hypovolaemic hyponatraemia**
    - **Diagnosis may supported by an elevated urea suggesting dehydration.**
    - **rehydration with sodium chloride 0.9%** or a balanced crystalloid (Hartmann's)
    - avoid rapid correction of sodium in order to reduce the risk of osmotic complications such as central pontine myelinolysis
      - ❖ The rate of correction of hyponatremia should not exceed **eight** mEq/L per day.

- ⇨ **Euvolaemic hyponatraemia**
  - check urine and serum osmolality. Does the patient meet the criteria for SIADH?
  - treat the underlying cause where possible in SIADH
  - fluid restriction (500-750mls/day)
  - monitor fluid balance and perform daily weights
  - consider demeclocycline or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone.
- ⇨ **Hypervolaemic hyponatraemia**
  - fluid and salt restriction
  - consider diuretics
  - treat the underlying cause (e.g. cardiac failure)

Hyponatraemia: correction

Acute hyponatraemia is that which occurs within a duration of 48 hours.

Acute hyponatraemia

- predisposing factors to acute hyponatraemia:
  - ⇨ Over consumption of fluids,
  - ⇨ prolonged race duration and inadequate training
- Pathophysiology
  - ⇨ When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result patients may die from brain herniation.
- Treatment
  - ⇨ The correct treatment to give is hypertonic saline.
  - ⇨ Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment.
  - ⇨ A small, quick increase in the serum sodium is required in order to decrease intracranial pressure. **Hypertonic saline (3%) boluses are the most appropriate treatment to improve neurological status in such patients.**

Hyponatremia in patients with advanced cirrhosis

- **Mechanism**
  - ⇨ **systemic vasodilation**,(The most important factor) which leads to activation of endogenous vasoconstrictors including antidiuretic hormone (ADH); ADH promotes the water retention that is responsible for the fall in serum sodium.
- Tolvaptan (Vasopressin receptor antagonists) should not be used in patients with cirrhosis, because of its known potential for hepatotoxicity.

Central pontine demyelinolysis

Central pontine myelinolysis (CPM):
- **Due to rapid correction of hyponatraemia**
- **the classical presentation is spastic quadriparesis, pseudobulbar palsy, and emotional lability (pseudobulbar affect) (locked in syndrome.)**

- **Definition:** damage to the myelin sheath of the white matter in the CNS caused by a sudden rise in serum osmolality (rapid correction of chronic hyponatremia)
- Affects the central region of the pons
- **Pathophysiology:** rapid sodium correction → Sudden rises in plasma osmolarity → fluid shift from the cerebral intracellular space to the extravascular space (**loss of water from the intracellular compartment**) → cerebral shrinking and demyelination → end result is central pontine myelinolysis (CPM).
- **Features**
  - ⇨ Symptoms first develop several days after the correction of hyponatremia.
  - ⇨ Central pontine myelinolysis
    - Altered level of consciousness, including coma
    - Locked-in syndrome
    - Impaired cranial nerve function: dysarthria, dysphagia, and diplopia
    - Worsening quadriparesis
- **Diagnosis**: MRI brain
- **Treatment:** supportive care
- **Prevention:** Avoid hypernatremia
  - ⇨ Many authorities recommend that increases in serum sodium of **<12 mmol/24 hours** are likely to be safe for the majority of patients.
  - ⇨ Certain patients with hypokalaemia, liver disease, poor nutritional state or burns are at higher risk of demyelination and should have a rate of sodium correction of **<8 mmol/24 hours.**

"Saline depletion, for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's."

Osmolar gap

- **Osmolar gap is the difference between the calculated osmolarity and the measured osmolality.**
- The normal value is 10-15 but may be increased in the presence of unmeasured 'abnormal' osmotically active ions in the plasma.
- An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute that may be present in significant amounts.
- Ethanol, ethylene glycol (anti-freeze), acetone and methanol are solutes that will cause elevation of the osmolar gap in this way.
- **Calculated osmolarity = 2 (Na + K) + Glucose + Urea (all in mmol/L).**
- Normal serum osmolarity is 285-295 mOsm/L.
- **Osmolality is measured in the laboratory using an osmometer.**

Hypomagnesaemia

Definition

- Low magnesium below 0.7 mmol/L .

Overview

- Normal plasma magnesium (0.7-0.9 mmol)
- **The thick ascending limb (TAL) of the loop of Henle is the major site of reabsorption (60-70%)** (unlike most ions, those reabsorbed in the proximal convoluted tubule)
- **In the TAL, magnesium is** passively reabsorbed. In the distal convoluted tubule, magnesium is reabsorbed via an active, transcellular **TRPM6** channel .

Uses for magnesium include:

- polymorphic ventricular tachycardia (torsade de pointes),
- acute asthma
- prevention/treatment of seizures in pre-eclampsia.
- **Magnesium salts can be given as laxatives**

Causes of low magnesium

- **Inadequate intake:**
  - ⇨ Malnutrition, and
  - ⇨ Alcohol dependence. Hypomagnesemia is the most common electrolyte abnormality observed in alcoholic patients
  - ⇨ **Total parenteral nutrition**
- **Malabsorption:**
  - ⇨ Inflammatory bowel disease
  - ⇨ Long term PPI therapy
  - ⇨ Gluten enteropathy
  - ⇨ Intestinal bypass, and
  - ⇨ Radiation enteritis.
- **Renal tubular disease:**
  - ⇨ Hyperaldosteronism
  - ⇨ Hyperparathyroidism
  - ⇨ Obstructive uropathy
  - ⇨ Potassium depletion, and
  - ⇨ Drugs (including diuretics, amphotericin, cisplatin, ciclosporin, amikacin, gentamicin, laxatives, and tacrolimus).
- **Intracellular shift:**
  - ⇨ Post myocardial infarction
  - ⇨ Post parathyroidectomy
  - ⇨ Recovery from diabetic ketoacidosis (K^+ and PO_4^- also enter cells)
  - ⇨ Refeeding syndrome (PO_4^- also enters cells),
  - ⇨ Acute pancreatitis.

- **Drugs:**
  - ⇨ **cisplatin**
  - ⇨ **diuretics**
  - ⇨ **cyclosporine**
  - ⇨ **cardiac glycosides**
  - ⇨ **Colorectal cancer treatment with cetuximab/panitumumab (EGF receptor inhibitors) → ↓ TRPM6 → hypomagnesemia.**
  - ⇨ **Omeprazole → hypomagnesaemia** → hypoparathyroidism → hypocalcaemia.
- Diarrhoea
- Metabolic acidosis
  - ⇨ Chronic metabolic acidosis → ↓renal TRPM6 expression in the DCT → ↓ Mg reabsorption →↓ serum Mg.
- **Hypercalcaemia**
  - ⇨ Hypercalcemia → activation of **calcium-sensing receptor (CaSR) →** ↓ Mg reabsorption
- Hypokalaemia, hypocalcaemia
- **Genetic diseases**

Features

- **General**
  - ⇨ **lack of appetite.**
  - ⇨ **Lethargy**
  - ⇨ **fatigue**
- **neuromuscular hyper-excitability**
  - ⇨ **muscle weakness including fasciculations**
  - ⇨ **changes in personality**
  - ⇨ **paraesthesia**
  - ⇨ **tetany**
  - ⇨ **seizures**
- cardiac
- **arrhythmias**
- **ECG features similar to those of hypokalaemia**
- The ECG change most typically associated with hypomagnesaemia is QT prolongation.
- **exacerbates digoxin toxicity**
- **decreased PTH secretion → hypocalcaemia**
- **Hypokalemia (in 40-60%)**

Associations with hypomagnesemia

- Hypoparathyroidism
  - ⇨ ↓ Mg →↓ magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP) → ↓PTH → hypoparathyroidism
- DM (↓ Mg →↓ insulin sensitivity and secretion)
- Cardiac: CAD, Hypertension (Mg plays a role in BP regulation), cardiac arrhythmia (prolongation of the QT interval , Torsade de pointes)

Investigation

- blood magnesium levels can guide but do not accurately reflect total body magnesium status. Attempts to find a marker of cellular magnesium status include measuring erythrocyte or monocyte Mg but these are not generally available.
- Urine Mg excretion is a useful guide. When there is inadequate intake or malabsorption, the kidneys would normally conserve Mg, giving urine Mg concentrations <7 mmol/24 hours. The reference range is around 2-7 mmol/24 hours.

Treatment

- <0.4 mmol/l
  - ⇨ intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours
- >0.4 mmol/l
  - ⇨ oral magnesium salts (10-20 mmol orally per day)
  - ⇨ diarrhoea can occur with oral magnesium salts

Hypermagnesaemia

Overview

- Hypermagnesaemia is much less common than hypomagnesaemia and is often iatrogenic in cause.

Causes of hypermagnesaemia

- **Iatrogenic:**
  - ⇨ Treatment with magnesium sulphate to prevent/treat seizures in patients with eclampsia or pre-eclampsia
  - ⇨ Treatment with Mg containing antacids
  - ⇨ Use of citrate-glucuronic acid solutions to dissolve renal calculi either through bladder irrigation or via a nephrostomy tube
  - ⇨ Over-zealous IV treatment of hypomagnesaemia
  - ⇨ Chronic use of Mg-containing enemas.
- **Other causes:**
  - ⇨ **Acute or chronic renal failure**
    - release of Mg from tissues,
    - Mg in dialysate,
    - Mg in phosphate binding drugs
  - ⇨ Familial hypocalciuric hypercalcaemia.

Lithium can cause hypermagnesaemia

Features

- Mild hypermagnesemia often asymptomatic
- Nausea, Lethargy
- Reduced deep tendon reflexes
- Blurry vision
- Cardiac: Vasodilatation, Hypotension, Bradycardia
- ECG changes: ↑ PR interval, ↑ QRS duration, ↑ QT interval
- Blurry vision
- Hypocalcemia
- Severe hypermagnesemia
  - ⇨ Muscle paralysis (flaccid quadriplegia)
  - ⇨ Bradycardia, Cardiac arrest
  - ⇨ Respiratory failure

Treatment

- If mild/moderate and iatrogenic, often it is enough to identify and stop the cause.
- In an emergency, dialysis or administration of IV calcium glucuronate (10 ml of 10%) will reduce the effects of hypermagnesaemia.

Hypophosphataemia

Definition

- serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L).

Causes

Causes	Consequences
• alcohol excess • acute liver failure • diabetic ketoacidosis • refeeding syndrome • **primary hyperparathyroidism** • **osteomalacia** • **Hyperventilation**	• red blood cell haemolysis • white blood cell and platelet dysfunction • muscle weakness and rhabdomyolysis • central nervous system dysfunction

Mechanisms

- The three major mechanisms of hypophosphataemia are:
  1. Redistribution of extracellular phosphate into cells
     - **hyperventilation** → respiratory alkalosis → activating phosphofructokinase → moves phosphate into cells → stimulates intracellular glycolysis.
     - Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced.
     - Any cause of hyperventilation (eg, sepsis, **anxiety**, **pain**, heatstroke, alcohol withdrawal, diabetic ketoacidosis [**DKA**], hepatic encephalopathy, salicylate toxicity, neuroleptic malignant syndrome [NMS]) can precipitate hypophosphatemia.
  2. Decreased intestinal absorption,
     - chronic diarrhea,
     - malabsorption syndromes,
     - severe vomiting,
     - nasogastric (NG) tube suctioning.
  3. Depletion due to increased urinary loss.
     - the most common cause of hypophosphatemia
       - primary and secondary hyperparathyroidism.
       - Osmotic diuresis, such as seen in hyperosmolar hyperglycemic syndrome (HHS)
       - Fanconi syndrome (proximal tubule dysfunction)
       - X linked hypophosphataemic rickets
       - Oncogenic hypophosphataemic osteomalacia

MRCPUK- part-1-Sep 2017: what is the mechanism of Hypophosphataemia during treatment of DKA?

→ **Shift from extracellular to intracellular space**

MRCPUK-part-1-Sep 2017: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission ?

→ **Shift from extracellular to intracellular space**

- The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.
- Two factors may contribute to this shift:
  1. I.V therapy with dextrose-containing solutions or refeeding → ↑Glucose → ↑ insulin release → ↑ phosphate uptake by the cells
  2. alcohol withdrawal → hyperventilation →acute respiratory alkalosis →intracellular alkalosis → stimulates intracellular phosphofructokinase →↑ glycolysis → movement of phosphate into cells

Hyperphosphataemia

Overview

- The healthy adult usually ingests about **8400 mg per week of phosphate through their diet**
- **Absorption** occurs mainly in the jejunum
- **Renal reabsorption:** the **majority** (70%) of filtered phosphate is reabsorbed by **type 2a sodium phosphate cotransporters** located on the apical membrane of the renal **proximal tubule**.
- **The normal adult range** for phosphorus is 2.5-4.5 mg/dL (0.81-1.45 mmol/L).
- **Renal excretion : About 5400 mg of phosphate is excreted per week through the kidneys.**

Causes

- Usually iatrogenic
- ↓calcium + ↑ phosphate levels seen in (**decreased phosphate excretion**)
  - ⇨ **renal failure**
  - ⇨ hypoparathyroidism, and pseudohypoparathyroidism
- ↑calcium + ↑phosphate seen in
  - ⇨ **vitamin D intoxication** (↓PTH + ↑ vitamin D)
  - ⇨ milk-alkali syndrome (↓PTH + ↓vitamin D)
- **Disorder that shifts intracellular phosphate to extracellular space**
  - ⇨ Tumor lysis
  - ⇨ Rhabdomyolysis
- **Increased phosphate intake** (e.g., phosphate-containing enemas)
  - ⇨ Laxative (Phospho-soda) abuse
  - ⇨ **Foods that are characteristically rich in phosphate include: dairy products, (Cheddar cheese),** fibre rich foods, chocolate, and processed meats.

Features

- Often asymptomatic
- High PO43- levels cause the formation of an insoluble compound with calcium, which can lead to:
  - ⇨ Hypocalcemia → hypocalcemic symptoms (muscle cramps, tetany, and perioral numbness or tingling).
  - ⇨ Nephrolithiasis
  - ⇨ Calcifications in the skin

Management

- Treat the underlying cause.
- Discontinue phosphate intake (dietary or medication).
- Give phosphate binders (e.g., aluminium hydroxide, calcium carbonate).
- Consider dialysis (especially in severe cases of hyperphosphatemia in patients with renal failure).

Vitamin B3 (Niacin) Deficiency

Causes

1. **Malnutrition**:
   - Poor dietary intake of niacin or its precursors.
2. **Alcoholism**:
   - Common in heavy drinkers due to inadequate intake and absorption.
3. **Tryptophan Deficiency Conditions**:
   - **Hartnup disease**: Decreased renal and intestinal tryptophan absorption.
   - **Carcinoid syndrome**: Increased tryptophan metabolism into serotonin.
4. **Vitamin B6 Deficiency**:
   - Impaired conversion of tryptophan to niacin (e.g., due to isoniazid treatment).
5. **Chronic Grain Consumption**:
   - Diets reliant on grains not processed by **nixtamalization** (lime-water soaking) fail to release niacin.

Clinical Features

1. **Atrophic Glossitis**:
   - Tongue appears pink or red, smooth, and glossy due to papillae atrophy.
   - May cause pain and discomfort.
2. **Pellagra** (Severe Deficiency):
   - **Dermatitis**:
     - Circular rash on the neck (Casal's necklace; affects C3–C4 dermatomes).
     - Hyperpigmented lesions on sun-exposed skin (e.g., limbs).
   - **Gastrointestinal Symptoms**:
     - Diarrhoea and vomiting.
   - **Neurologic Symptoms**:
     - Dementia, hallucinations, anxiety, insomnia, encephalopathy.

Pellagra

- **The classical features are the 3 D's - Dermatitis, Diarrhoea and Dementia.**
- **Caused by nicotinic acid (niacin) deficiency.**

Vitamin C Deficiency (Scurvy)

Overview

- **Vitamin C (Ascorbic Acid)**:
  - A water-soluble vitamin.
  - Dehydroascorbic acid (oxidative form) is the preferred cellular form for erythrocytes and leukocytes.

Functions

1. **Antioxidant**:
   - Provides electrons for reducing molecular oxygen.
   - Stabilizes **vitamin E** and **folic acid**.
2. **Collagen Synthesis**:
   - Cofactor for enzymes involved in hydroxylation of proline and lysine.
   - Deficiency → defective collagen synthesis → capillary fragility, poor wound healing.
3. **Folate Metabolism**:
   - Cofactor for reduction of folate to dihydro- and tetrahydrofolate.
   - **Macrocytic anaemia in scurvy**:
     - Due to oxidative haemolysis and impaired folate metabolism.
4. **Iron Absorption**:
   - Enhances non-heme iron absorption.
5. **Neurotransmitter Synthesis**:
   - Cofactor for norepinephrine synthesis.

Causes

- Poor dietary intake:
  - Little or no fruits and vegetables (e.g., "tea and toast" diet in alcoholics or elderly).
- Increased requirements:
  - **Pregnancy**, **lactation**, **thyrotoxicosis**.

Clinical Features

1. **Early Signs**:
   - Gingivitis, bleeding gums.
   - Loose teeth.
   - Poor wound healing.
   - General malaise, fatigue.
   - Anaemia:
     - **Macrocytic anaemia**: Due to oxidative haemolysis and folate metabolism defects.
     - **Normochromic, normocytic anaemia**: Reflects tissue bleeding.
2. **Progressive Symptoms**:
   - Anaemia, myalgia, bone pain.
   - Bruising, petechial and perifollicular haemorrhages.
   - Corkscrew hairs, mood changes, fragility.
   - Scleral icterus (secondary to haemolysis), pale conjunctiva.
   - Bleeding into muscles and joints.
   - In children: Fractures, dislocations, bone tenderness.

3. **Late Stages**:
    - Generalised oedema, severe jaundice.
    - Haemolysis, haemorrhage.
    - Neuropathy, convulsions.
    - Death.
4. **Skin Manifestations**:
    - Perifollicular hyperkeratotic papules.
    - Perifollicular haemorrhages.
    - Purpura, ecchymoses.

Treatment
- **Vitamin C Supplementation**:
    - Recovery is usually complete within three months.

Vitamin B12 Deficiency
Overview
- **Function**: Essential for red blood cell development and nervous system maintenance.
- **Absorption**:
    - Requires intrinsic factor (IF) secreted by stomach parietal cells.
    - Absorbed in the terminal ileum.
    - Small amounts passively absorbed without IF (~1% of large doses).
- **Transport**: Binds to transcobalamin II for body distribution.
- **Storage**: Depletion occurs after 12–15 years of deficiency.

Causes
1. **Malabsorption**:
    - ↓ Intrinsic Factor:
        - Autoimmune atrophic gastritis (most common).
        - H. pylori infection.
        - Gastrectomy.
    - Reduced uptake of IF-Vitamin B12 complex in the terminal ileum:
        - Alcohol use disorder, Crohn's disease, celiac disease.
        - Pancreatic insufficiency.
        - Surgical ileum resection.
        - Diphyllobothrium latum (tapeworm) infection.
        - Bacterial overgrowth, enteritis, achlorhydria.
2. **Malnutrition**:
    - Strict vegan diets (deficiency develops after years of exclusivity).
3. **Increased Demand**:
    - Pregnancy, breastfeeding.
    - Chronic metformin use (~30% of cases).

Clinical Features
- **Haematological**:
    - Macrocytic anaemia.
    - Sore tongue and mouth.

- **Neurological**:
  - Peripheral neuropathy.
  - Subacute combined degeneration of the spinal cord.
  - Can occur without anaemia.
  - Autonomic dysfunction (e.g., impotence, incontinence).
- **Psychiatric**:
  - Impaired memory, depression, dementia, irritability, rare psychosis.
- **Cardiovascular**:
  - Hyperhomocysteinemia (independent risk factor for atherosclerosis).
  - Associated with coronary artery disease.

Investigations

1. **Initial Test**:
   - Serum cobalamin levels (may miss subclinical deficiency).
2. **More Sensitive Tests**:
   - **Methylmalonic acid** (↑ early in B12 deficiency; more specific).
   - **Homocysteine** (↑ in B12 or folate deficiency).
   - Folic acid levels (check in hyperhomocysteinemia cases).
3. **Enzymatic Reactions**:
   - **Methylmalonic acid** → succinyl-CoA (Vitamin B12-dependent).
   - **Homocysteine** → methionine (Vitamin B12 and folic acid-dependent).

Management

1. **Without Neurological Symptoms**:
   - IM hydroxocobalamin: 1 mg 3×/week for 2 weeks, then once every 3 months.
   - Oral Vitamin B12: 1,000–2,000 mcg/day (effective in pernicious anaemia and other deficiency states).
2. **With Folic Acid Deficiency**:
   - Treat B12 first to avoid precipitating **subacute combined degeneration of the cord**.
   - Folic acid alone may correct anaemia but not neurological damage.

Sep 2017 part 1: Which structure in the body are able to synthesize vitamin B12?

➲ **gut bacteria**

- It is synthesized by gut bacteria in humans, but humans cannot absorb the B_{12} made in their guts, as it is made in the colon which is too far from the small intestine, where absorption of B_{12} occurs.
- Therefore diet is the only source of vit B12.

Vitamin B1 (Thiamine) Deficiency

Overview
- **Active Form**: Thiamine pyrophosphate (TPP).
- **Biochemical Role**:
  - Required in glycolysis and the tricarboxylic acid (TCA) cycle.
  - Functions as a cofactor for these enzymes:
    1. **α-ketoglutarate dehydrogenase**.
    2. **Branched-chain amino acid dehydrogenase**.
    3. **Pyruvate dehydrogenase**.

Causes
- Heavy alcohol drinking.
- Malnutrition or starvation.
- Malabsorption syndromes.
- Malignancy.

Pathophysiology
- **Mechanism**:
  - Thiamine deficiency → impaired glucose breakdown → reduced ATP production → tissue damage in highly aerobic organs (e.g., brain, heart).
- **Complications**:
  - High-dose glucose infusion without prior thiamine → worsened ATP depletion → triggers **Wernicke encephalopathy** in malnourished individuals or alcohol users.

Clinical Features
1. **Beriberi**:
   - Caused by inadequate thiamine intake.
   - Types:
     - **Dry Beriberi**:
       - Symmetrical peripheral neuropathy (sensory and motor).
       - Progressive muscle wasting.
       - Paralysis and confusion.
     - **Wet Beriberi**:
       - Oedema.
       - High-output cardiac failure (dilated cardiomyopathy).
2. **Wernicke Encephalopathy**:
   - Classic triad: **Encephalopathy**, **Ataxia**, **Oculomotor dysfunction** (e.g., nystagmus).
3. **Korsakoff's Psychosis**:
   - Anterograde and retrograde amnesia with **confabulation**.

Why Thiamine Must Precede Glucose Infusion
- **Without thiamine**:
  - Pyruvate cannot enter the TCA cycle → pyruvate accumulates → converted to lactate → **lactic acidosis**.
  - Impaired pentose phosphate pathway → increased **reactive oxygen species** → cellular damage or apoptosis.

Vitamin Cofactors Summary

- **Thiamine**: Required for dehydrogenase reactions.
- **Biotin**: Cofactor for carboxylase reactions.
- **Vitamin B9 (Folate)**: Essential for transferases.
- **Vitamin C**: Functions as a cofactor for hydroxylases.

Vitamin E Deficiency

Active Form

- Tocopherol.

Function

- Lipid-soluble antioxidant in the **glutathione peroxidase pathway**:
  - Removes free radical intermediates.
  - Protects cell membranes from oxidative damage by reacting with lipid radicals in the lipid peroxidation chain reaction.

Therapeutic Uses

- Nonalcoholic steatohepatitis (NASH).

Clinical Features

1. **Neurologic Dysfunction**:
   - **Pathophysiology**: Demyelination of the posterior column and spinocerebellar tract.
   - **Symptoms**:
     - ↓ Proprioception and vibration sensation.
     - Ataxia.
   - Resembles vitamin B12 deficiency but **lacks**:
     - Hypersegmented neutrophils.
     - Megaloblastic anaemia.
     - ↑ Methylmalonic acid levels.
2. **Haematologic Effects**:
   - **Hemolytic Anaemia**: Increased erythrocyte fragility and membrane breakdown.
   - **Acanthocytosis**: Presence of spur cells in the blood.
3. **Muscle Weakness**:
   - Likely due to oxidative damage to muscle cell membranes.

Hypervitaminosis E

- **Complications**:
  - Interferes with vitamin K metabolism.
  - Results in **vitamin K deficiency**, leading to an **increased tendency to bleed**.

Vitamin K Deficiency

Sources

1. **Dietary**: Leafy green vegetables (**Vitamin K1**).
2. **Synthesis**: Small amounts produced by intestinal bacteria.

Functions

1. **Coagulation**:
   - Cofactor for **γ-carboxylation** of glutamate residues.
   - Essential for the activation of:
     - **Coagulation factors**: II (prothrombin), VII, IX, X.
     - **Anticoagulants**: Protein C and Protein S.
2. **Bone Formation**:
   - Required for **osteocalcin** (bone Gla protein) and **matrix Gla protein**.

Causes

- **Liver Failure**: Impairs vitamin K activation.
- **Fat Malabsorption**: Reduced absorption of fat-soluble vitamins (e.g., pancreatic insufficiency, biliary obstruction).
- **Prolonged Broad-Spectrum Antibiotic Therapy**: Disrupts intestinal bacteria.
- **Vitamin K Antagonists**: e.g., **warfarin**.

Clinical Features

1. **Haemorrhage**:
   - Petechiae, ecchymoses.
   - **Vitamin K Deficiency Bleeding (VKDB)**:
     - Common in newborns (due to low stores at birth).
     - Presents with ↑ **PT** and **aPTT**, but normal **bleeding time**.
2. **Postnatal Prophylaxis**:
   - Vitamin K injection at birth to prevent VKDB.

Vitamin A Deficiency

Overview

- **Active Forms**: Retinal and Retinoic acid.
- **Sources**:
  - **Plant-based**: Yellow and leafy vegetables.
  - **Animal-based**: Liver (storage form).

Causes

- Disorders associated with **fat malabsorption**:
  - **Inflammatory bowel diseases** (e.g., Crohn's disease).
  - **Celiac disease**.
  - **Cystic fibrosis**.
  - **Pancreatic insufficiency**.

Clinical Features

1. **Ocular Manifestations**:
   - **Night blindness (nyctalopia)**.
   - **Xerophthalmia** (dry eyes).
   - **Keratomalacia** (corneal softening).
   - **Bitot spots**:
     - Gray, triangular, dry patches on the bulbar conjunctiva.
     - Foamy appearance due to squamous metaplasia and keratinization.
     - **Typical sign of vitamin A deficiency**.

2. **Other Features**:
   - **Keratinizing squamous metaplasia**:
     - Bladder: Pearl-like plaques on cystoscopy.
   - **Xerosis cutis** (dry skin).
   - **Immunosuppression**:
     - Increased susceptibility to infections.

Vitamin A Toxicity

1. **Causes**: Excess intake through supplements or drugs.
2. **Types**:
   - **Acute Toxicity**:
     - Nausea, vomiting.
     - Vertigo, blurred vision.
   - **Chronic Toxicity**:
     - Alopecia, dry scaling skin.
     - Arthralgias.
     - Hepatosplenomegaly, hepatic toxicity.
     - Pseudotumor cerebri (increased intracranial pressure).

Special Considerations

1. **Correcting Visual Disturbance**:
   - **Substance**: Retinaldehyde (derived from the oxidation of retinol).
2. **Wound Healing in Long-term Steroid Use**:
   - **Vitamin A**:
     - Stimulates TGF-beta, IGF-I, and collagen production.
     - Counteracts the inhibitory effect of steroids on wound healing.
     - Caution: High doses can be toxic and inhibit collagen synthesis.

Vitamin and Selenium Deficiency

Vitamin	Chemical Name	Deficiency State
A	Retinoids	- Night blindness (nyctalopia). - Dry skin.
B1	Thiamine	**Beriberi**: - Polyneuropathy. - Wernicke-Korsakoff syndrome. - Heart failure (dilated cardiomyopathy).
B2	Riboflavin	- Angular stomatitis. - Cheilosis. - Corneal vascularization.
B3	Niacin	**Pellagra**: - Dermatitis. - Diarrhoea. - Dementia.
B6	Pyridoxine	- Anaemia. - Irritability. - Seizures.
B7	Biotin	- Dermatitis. - Seborrhoea.

Vitamin	Chemical Name	Deficiency State
B9	Folic acid	- Megaloblastic anaemia. - Neural tube defects (in pregnancy).
B12	Cyanocobalamin	- Megaloblastic anaemia. - Peripheral neuropathy.
C	Ascorbic acid	**Scurvy**: - Gingivitis. - Bleeding. - Poor wound healing.
D	Ergocalciferol, Cholecalciferol	- Rickets (children). - Osteomalacia (adults).
E	Tocopherol, Tocotrienol	- Increased fragility of RBCs. - Mild haemolytic anaemia (newborns). - Ataxia, peripheral neuropathy.
K	Naphthoquinone	- Haemorrhagic disease of the newborn. - Bleeding diathesis.
Selenium	Selenium	- Keshan disease (cardiomyopathy).

Zinc deficiency

Aspect	Details
Overview	- Essential trace element. - Required for enzyme function, immune response, and growth.
Sources	- Red meat, shellfish, legumes, seeds, nuts.
Functions	- Cofactor for over 300 enzymes. - Supports DNA synthesis, cell division, and immunity. - Promotes wound healing. - Essential for growth and vision.
Causes	- **Dietary deficiency**: Inadequate intake, vegetarian/vegan diets (high phytates). - **Malabsorption**: Crohn's disease, celiac disease, short bowel syndrome. - **Increased requirements**: Pregnancy, growth periods. - **Excessive loss**: Chronic diarrhea, burns, nephrotic syndrome. - **Alcoholism**: Impairs absorption and increases excretion. - **Genetic**: Acrodermatitis enteropathica.
Clinical Features	- **Dermatological**: Alopecia, **dermatitis (perioral/perianal),** dry or scaly skin. - **Immune**: Increased infections (respiratory, gastrointestinal). - **Gastrointestinal**: Loss of appetite, diarrhea. - **Growth**: Retardation in children, delayed wound healing. - **Neurological**: Irritability, depression, cognitive dysfunction. - **Other**: Hypogonadism, impaired taste (dysgeusia) and smell (anosmia), night blindness.
Diagnosis	- **Clinical**: Based on symptoms. - **Laboratory**: Low serum zinc levels (<70 mcg/dL), low alkaline phosphatase activity.
Management	- **Dietary**: Increase intake of zinc-rich foods. - **Supplementation**: Oral zinc (10–40 mg/day based on severity). - **Underlying causes**: Treat malabsorption or other contributing conditions. - **Acrodermatitis enteropathica**: Lifelong zinc supplementation.

Pyruvate kinase

- **Pyruvate kinase is the rate-limiting step in glycolysis** and gluconeogenesis
- It catalyses the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding a molecule of pyruvate and a molecule of ATP
- **Deficient pyruvate kinase activity may result in the development of hereditary haemolytic anaemias**

Pyruvate Kinase Deficiency:

- **Pathophysiology**:
  - Autosomal recessive condition affecting the RBC isoform.
  - Reduced ATP production → impaired ion transport → **RBC hemolysis**.
- **Features**:
  - **Chronic haemolytic anaemia** (non-spherocytic).
  - Splenomegaly.
  - Jaundice.
  - Gallstones (due to chronic haemolysis).
- **Diagnosis**:
  - Decreased pyruvate kinase activity in RBCs.
  - Peripheral blood smear: Normocytic anaemia with polychromasia.
- **Management**:
  - Supportive care: Transfusions, folic acid supplementation.
  - Splenectomy in severe cases to reduce haemolysis.

Energy Creation in Long-Distance Running

- **Primary Energy Source**:
  - **Fatty Acid Oxidation becomes the dominant energy source during prolonged exercise (>20–30 minutes) when glycogen stores start depleting.**
  - This process occurs in the mitochondria and involves the breakdown of triglycerides into fatty acids and glycerol, followed by β-oxidation of fatty acids to generate **acetyl-CoA**, which enters the TCA cycle.
- **Aerobic Metabolism**:
  - Long-distance running is an **aerobic activity** that relies on **oxygen availability** for sustained energy production.
- **Fatty acids** provide more ATP per molecule compared to carbohydrates but require more oxygen for their metabolism.
- **Role of Glycogen**:
  - Glycogen is the primary fuel source during the **initial stages** of running.
  - As exercise continues, glycogen reserves are gradually depleted, leading to a **shift toward fat metabolism**.
- **Glycolysis**:
  - Important during the initial phase or for short bursts of energy.
  - Predominantly anaerobic in high-intensity activity.
- **Protein Oxidation**:
  - Contributes minimally to energy production during exercise, primarily in extreme conditions or when glycogen and fat stores are depleted.

Fatty acid oxidation is the primary contributor to energy creation during long-distance running.

4th edition

4th edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences

Genetics

Updated

2025

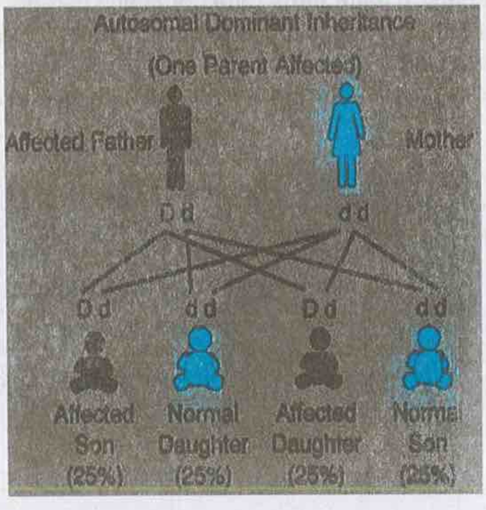
Autosomal dominant conditions

Key Characteristics

1. **Single Copy Mutation**:
   - Affected individuals have one mutated allele (heterozygous) and one normal allele.
   - The mutated allele dominates in determining the phenotype.
2. **Vertical Transmission**:
   - Trait or disorder is passed directly from one generation to the next.
   - No skipping of generations (unless due to reduced penetrance).
3. **Equal Gender Distribution**:
   - Both males and females are equally likely to inherit and transmit the condition.
4. **Recurrence Risk**:
   - Each child of an affected individual has a **50% chance** of inheriting the mutation, irrespective of gender.
5. **Penetrance and Expressivity**:
   - **Penetrance**: The likelihood that a person with the mutation shows symptoms of the disorder (e.g., reduced penetrance means not all carriers are affected).
   - **Expressivity**: The degree to which the phenotype is expressed (e.g., symptoms may vary in severity among affected individuals).

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- **some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant**
- **some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive**



The following conditions are autosomal dominant:

• **Achondroplasia** • Acute intermittent porphyria • Adult polycystic disease • Antithrombin III deficiency • Ehlers-Danlos syndrome • Familial adenomatous polyposis • Hereditary haemorrhagic telangiectasia • Hereditary spherocytosis • Hereditary non-polyposis colorectal carcinoma • Huntington's disease • Hyperlipidaemia type II • Hypokalaemic periodic paralysis	• Malignant hyperthermia • Marfan's syndromes • Myotonic dystrophy • Neurofibromatosis • **Noonan syndrome** • Osteogenesis imperfecta • Peutz-Jeghers syndrome • Retinoblastoma • Romano-Ward syndrome • **Tuberose sclerosis** • Von Hippel-Lindau syndrome • Von Willebrand's disease (type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease)

Chance of Passing a Disease in Autosomal Dominant Inheritance

1. **Each child of an affected individual** has a **50% chance** of inheriting the disease-causing mutation and thus developing the disorder, regardless of gender.
2. **Key Points**:
   - The unaffected child will not carry the mutation and cannot pass it on to their offspring.
   - If the affected individual has a new mutation (de novo), the chance of passing it on to their children is still **50%**.

Why 50%?

- Humans have **two copies of each gene** (one from each parent).
- An affected individual with one normal gene and one mutated gene (heterozygous) passes **one gene copy** to each child.
- The probability of passing the mutated or the normal gene is **1 in 2 (50%)**.

Examples

Scenario	Chance of Passing the Disorder
One parent affected	50% for each child.
Both parents affected	- 25% chance of being unaffected. - 50% chance of inheriting one mutated gene (affected). - 25% chance of inheriting two mutated genes (severe/life-threatening in some disorders).
No family history (de novo mutation)	0% for siblings but 50% for affected individual's children.

As an autosomal dominant condition, <u>two affected parents</u> can expect:

- **1 in 4 chance of an unaffected child**
- 1 in 2 chance of an affected heterozygous child
- 1 in 4 chance of an affected homozygous child.

Exceptions

- **Reduced Penetrance**: Even if the mutation is inherited, the individual may not express the disease phenotype.
- **Variable Expressivity**: Severity of symptoms can differ among those who inherit the mutation.

Which disease demonstrates autosomal co-dominant inheritance?
→ Alpha-1-antitrypsin deficiency

Achondroplasia

Aetiology

- **Mutation in fibroblast growth factor receptor 3 gene (FGFR3) → reduced endochondral ossification**
  - ⇨ activation of fibroblast growth factor receptor 3 on chromosome <u>4</u>, resulting in inhibited chondrocyte proliferation.
- **autosomal dominant**
- The homozygous form is usually fatal.

Epidemiology

- Most common type of skeletal dysplasia and disproportionate short stature (1:40,000 children worldwide affected)

Risk factor

- The incidence **increases with paternal age**.

Pathophysiology

- Epiphyseal growth cartilage fails,
- there is **normal bone formation and repair**.
  - ⇨ Therefore, **NO** increased risk of fracture.

Features

becomes obvious within the first year with disparity between a large skull, normal trunk length and short limbs.

- short stature
- short limbs (rhizomelia) with shortened fingers (brachydactyly)
  - ⇨ The fingertips may only come down to the iliac crest, and the shortness of the limbs is often most marked proximally.
  - ⇨ short stature due to shortening of the limbs, but spinal length is maintained.
  - ⇨ The limbs appear broad with deep creases.
- large head (Macrocephaly) with frontal bossing
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis
- Normal intelligence

Complications

- Small foramen magnum → compression of the cervical medulla
- Spinal canal stenosis and radiculopathy (of the lower back)
  - ⇨ low back and leg pain,
  - ⇨ paresthesias, dysesthesia,
  - ⇨ incontinence
- Secondary scoliosis
- **Recurrent otitis media**
- Cardiopulmonary complications (due to a small chest wall)

Diagnostics

- **X-ray**
  - ⇨ **It may be diagnosed radiographically at birth**,
  - ⇨ Lateral skull
    - midface hypoplasia,
    - frontal prominence
  - ⇨ pelvis
    - narrow in anteroposterior diameter with deep sacroiliac notches and short iliac wings.
  - ⇨ Spine
    - progressive narrowing of the interpedicular distance from top to bottom (reverse of normal).
      - ❖ abnormally narrow interpedicular distance → spinal canal stenosis; scoliosis
  - ⇨ Extremities
    - bones are short and broad;
    - short fingers
    - metaphyseal irregularity,
    - flaring in the long bones,
    - late-appearing irregular epiphyses.

Management

- **Medical**
  - ⇨ Early administration of **growth hormone** (1–6 years)
- **Surgical corrections:**
  - ⇨ spinal stenosis, secondary scoliosis, genu varum, foramen magnum decompression

Osteogenesis imperfecta ("brittle bone disease")

Pathophysiology

- **Autosomal dominant mutation** in **COL**1A1 or **COL**1A2 genes → ↓ synthesis of normal type I collagen → impaired bone matrix formation (osteogenesis)

Features

- **Growth retardation**
- **Skeletal deformities, brittle bones, and recurrent fractures from minimal trauma**
- **Blue sclerae due to visible choroidal pigment.**
- **Progressive hearing loss** secondary to **otosclerosis**
- **Brittle, opalescent teeth** (dental imperfections) due to a lack of dentin formation.

Types

- type 1:The most common, and milder form.
- Type II: most severe form; lethal perinatally or within the first year

Diagnostics

- DNA test
- Ultrasonography before birth and radiographic skeletal survey afterwards (fractures, callus, deformities)
- **Bone or skin biopsy → type 1 collagen mutation**

Therapy

- No cure available
- Bisphosphonates; decrease the risk of fractures
- Surgery for functional improvement

Individuals with osteogenesis imperfecta can't BITE: Bones (recurrent fractures), I ("eye" = blue sclerae), Teeth (dental abnormalities), Ears (hearing loss).

MRCPUK-part-1-May-2009 exam: A pregnant woman is known to have polycystic kidney disease. What is the chance her child will also have the disease?
→ 50% (Polycystic kidney disease is usually inherited in an autosomal dominant fashion and hence 50% of her children will be affected, regardless of gender)

Down's syndrome (trisomy 21)

Epidemiology and genetics

- the most common autosomal abnormality

Risk of Down's syndrome with increasing maternal age

Age (years)	Risk
20	**1 in 1,500**
30	1 in 800
35	1 in 270
40	1 in 100
45	1 in 50 or greater

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age

Cytogenetics

Mode	% of cases	Risk of recurrence
Non-disjunction	**94%**	1 in 100 if under mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

- The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher.
- Down syndrome have one of the two karyotypes:
  1. 47,XX,+21 (trisomy 21): more common
  2. 46,XY,der(14;21): characterized by the presence of two normal chromosomes 21, one normal chromosome 14 and a product of Robertsonian translocation between chromosomes 14 and 21 (der(14;21); der stands for derivative).

The general risk of trisomy 21 increases with maternal age. This does not, however, apply to translocation trisomies

Features

- face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- flat occiput
- single palmar crease, pronounced 'sandal gap' between big and first toe
- hypotonia
- congenital heart defects (40-50%, see below)
- duodenal atresia **can be diagnosed by U/S at gestation → double bubble sign**
- Hirschsprung's disease

Associations

- **↑↑ risk for developing acute myeloid leukemia (AML)** (approximately 1-2% of children with Down syndrome develop AML, the great majority < 5 y) rather than acute lymphoblastic leukemia (ALL), which is a more common form of leukemia in children.
- Other haematological disorders associated with Down's syndrome include:
  - ⇨ Fanconi's anaemia,
  - ⇨ Patients with learning disabilities may be prone to lead poisoning due to pica.

Cardiac complications

- 50% of children with Down's syndrome have a cardiac defect.
- multiple cardiac problems may be present
- **endocardial cushion defect (c. 40%, also known as atrioventricular septal canal defects)**
- ventricular septal defect (c. 30%)
- secundum atrial septal defect (c. 10%)
- tetralogy of Fallot (c. 5%)
- isolated patent ductus arteriosus (c. 5%)

Later complications

- subfertility:
  - ⇨ Males are almost always infertile due to impaired spermatogenesis.
  - ⇨ **Females are usually subfertile,** and have an increased incidence of problems with pregnancy and labour
- learning difficulties
- short stature
- repeated respiratory infections (+hearing impairment from glue ear)
- acute lymphoblastic leukaemia
- hypothyroidism
- Alzheimer's
- atlantoaxial instability

> **To remember the most important features associated with Down syndrome, think of the 5 A's: Advanced maternal age, duodenal Atresia, Atrioventricular septal defect, AML/ALL, early onset of Alzheimer disease.**

Diagnosis

Screening tests (Prenatal)

- **Combined test** (first trimester) (11–13 weeks)
  - ⇨ Maternal serum
    - ↑ Beta human chorionic gonadotropin (β-hCG)
    - ↓ Pregnancy-associated plasma protein A (PAPP-A)
  - ⇨ Ultrasound
    - **Nuchal translucency; increases** due to the large amount of fluid collecting behind the neck
    - Short neck, thickened nuchal fold
    - Absent or hypoplastic nasal bone
    - Shortened middle phalanges of the fifth digits with clinodactyly
    - Shortened long bones (humerus, femur)
- **Quadruple test** (second trimester) (15–18 weeks)
  - ⇨ ↓ Free estriol
  - ⇨ ↓ Alpha-fetoprotein (AFP)
  - ⇨ ↑ Inhibin A
  - ⇨ ↑ β-hCG

Diagnostic tests (confirmatory test)

- Prenatal → Fetal karyotyping
  - ⇨ Chorionic villus sampling (9–14 weeks)
  - ⇨ Amniocentesis (15–22 weeks)
  - ⇨ Percutaneous umbilical cord sampling (18–22 weeks)
- Postnatal → Chromosome analysis

In the quadruple test, hCG and Inhibin A are both HIgh up (↑) and Estriol and α-fEtoprotein are both dEficient (↓).

Noonan's syndrome

Overview

- Relatively common, autosomal-dominant inherited disorder.
- Caused by activating mutations in multiple genes in the Ras/mitogen-activated protein kinase (RAS-MAPK pathway).
- The most commonly implicated gene is PTPN11. on chromosome 12
- Often thought of as the 'male Turner's',
- In contrast to Turner's syndrome, **the karyotype is normal**
- The majority of patients lead normal lives

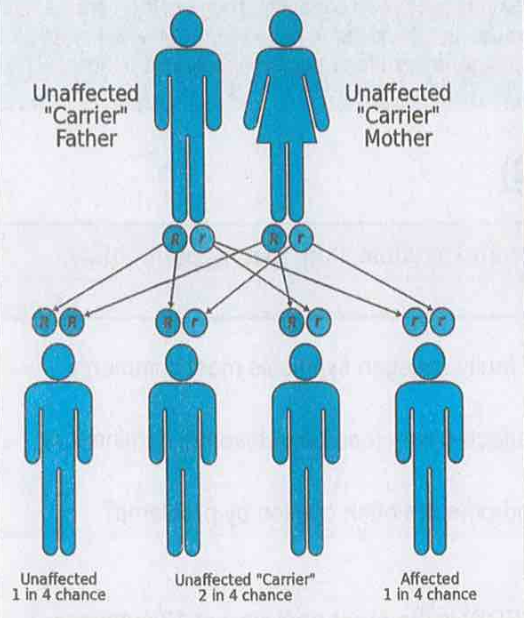
Feature

- features similar to Turner's syndrome:
  - ⇨ short stature,
  - ⇨ webbed neck,
  - ⇨ chest (pectus) deformity
    - widely-spaced nipples,
    - pectus carinatum and excavatum,
- characteristic features:
  - ⇨ cardiac: (occurs in 50% to 80%)
    - **typically, pulmonary valve stenosis**
    - **atrial septal defect (ASD)**
    - occasionally hypertrophic cardiomyopathy
  - ⇨ easy bruising or bleeding (due to coagulation factor deficiency or platelet dysfunction),
    - coagulation problems: factor XI deficiencies
  - ⇨ **facial features,**
    - triangular-shaped face
    - hypertelorism (increased distance between the eyes)
    - downslanting eyes
    - vivid blue or blue-green irides
    - low-set, posteriorly rotated ears
    - ptosis
  - ⇨ Boys frequently present with cryptorchidism and manifest delayed puberty.
  - ⇨ **learning disabilities**
    - Mild cognitive impairment is found in up to 33%
    - Intellectual development may be delayed, but by adulthood intelligence is normal in ⅔ of patients.

Autosomal recessive conditions

Key Characteristics

1. **Carrier Parents**:
   - Both parents are carriers (heterozygous) of the mutated gene but are unaffected.
   - Affected individuals inherit two mutated copies (homozygous).
2. **Risk of Inheritance**:
   - **25% chance**: Child is affected (inherits two mutated copies).
   - **50% chance**: Child is a carrier (inherits one mutated copy).
   - **25% chance**: Child is unaffected (inherits no mutations).
3. **Equal Gender Distribution**:
   - Both males and females are equally likely to inherit and express the disease.
4. **Skipping Generations**:
   - The condition can skip generations if no individual inherits two mutated copies.
   - Appears more commonly in **consanguineous families** (parents are related).



Two copies of the defective gene (one inherited from each parent) are required in order to be born with the disorder.

Autosomal recessive conditions are often thought to be **'metabolic'** as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some **'metabolic'** conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
- some **'structural'** conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

Autosomal recessive conditions are 'metabolic' - exceptions: inherited ataxias
Autosomal dominant conditions are 'structural' - exceptions: hyperlipidaemia type II, hypokalaemic periodic paralysis

The following conditions are autosomal recessive:

• Albinism • Ataxia telangiectasia • **Congenital adrenal hyperplasia** • Cystic fibrosis • Cystinuria • Familial Mediterranean Fever • Fanconi anaemia • Friedreich's ataxia • Glycogen storage disease	• Haemochromatosis • Homocystinuria • Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick • Mucopolysaccharidoses: Hurler's • PKU • Sickle cell anaemia • Thalassaemias • Wilson's disease

MRCPUK-part-1-May 2012 exam: A man diagnosed as having hereditary hemochromatosis. His wife is not a carrier. What is the chance his child will develop haemochromatosis?

➔ 0% (Haemochromatosis is an autosomal recessive condition. If one of the parents has haemochromatosis (i.e. is homozygous) and the other is not a carrier/affected, then all the children will inherit one copy of the gene from the affected parent and hence will be carriers)

Ehlers–Danlos syndrome (EDS)

The classic presentation of EDS involves hyperextensible skin, joint hypermobility, and a tendency to bleed easily.

- **Ehlers-Danlos syndrome** is a disorder of faulty collagen synthesis most commonly affecting collagen type III and V.
- Inheritance patterns and type of collagen affected vary (can be autosomal dominant or recessive)
- Collagen deficiencies in Ehlers-Danlos syndrome are often caused by problems with cross-linking.

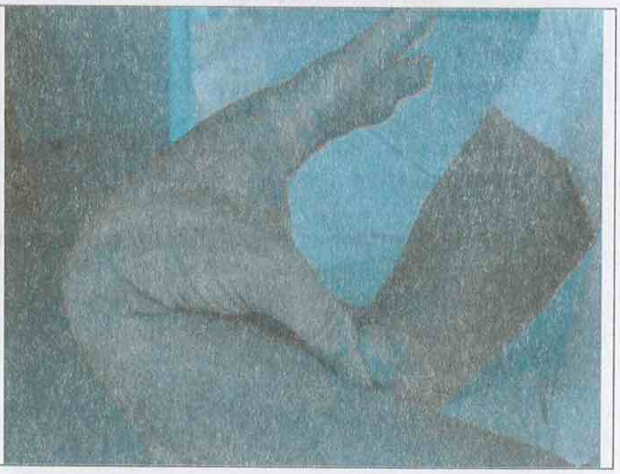
- **Hypermobile Ehlers-Danlos syndrome** (EDS) is the **most common** of 13 subtypes.
  - ⇨ Most hypermobile people are not aware of the fact and assume that everyone is as flexible as they are.
  - ⇨ Most cases of hypermobile EDS, are inherited in an autosomal dominant manner.
  - ⇨ associated with hypermobile joints, but skin features are much less prominent
  - ⇨ Systemic features may include increased propensity to asthma, mild valve regurgitation and gastrointestinal (GI) symptoms, including constipation and hiatus hernia.

- The <u>most severe</u> form of Ehlers-Danlos syndrome is the **<u>vascular</u> type**.
  - ⇨ deficiencies in type <u>III</u> collagen.
    - Type III collagen also known as reticulin, and is found primarily in granulation tissue, artery walls, skin, intestines and the uterus.
  - ⇨ involves vascular and organ rupture due to type III collagen deficiency.
- The **classical type** of Ehlers-Danlos syndrome has deficiencies in **type <u>V</u> collagen**.
  - ⇨ in which joint and <u>skin manifestations predominate</u>
    - associated with much <u>more severe dermatological features</u>, including hyperelastic skin that splits easily and marked propensity to bruising.
- **<u>Kyphoscoliotic EDS</u> is usually inherited in <u>autosomal recessive</u> fashion.**

Features

Cardiovascular	• Features of heart valve defects (particularly mitral valve prolapse) • Features of aneurysms/dissections of the iliac, splenic, renal arteries, or the aorta • Berry/saccular aneurysms of the cerebral arteries → features of subarachnoid hemorrhage
Musculoskeletal	• Joint hypermobility with tendency to dislocate • Skeletal abnormalities (e.g., scoliosis) • features of chronic pain syndrome and marfanoid habitus
Skin	• Tendency to bruise easily • Skin hyperextensibility • Frequent skin lacerations and poor skin healing (e.g., following surgery)
Other	• Hernias • Features of organ rupture (e.g., shock, local pain), especially in vascular EDS

Elbow region of a female patient of Ehlers-Danlos syndrome: The skin of the elbow is hyperelastic (cutis hyperelastica), but rapidly returns to its initial position when released.



Diagnosis

- Definitive diagnosis for <u>all subtypes of EDS</u>, except hypermobile EDS, can be made by molecular genetic testing.
- The genetic basis of <u>hypermobile EDS</u> remains unknown and the diagnosis is made by clinical criteria only.
- A baseline echocardiogram with views of the aortic arch and aorta and regular reevaluations should be obtained to evaluate for <u>mitral valve</u> prolapse and any signs of aortic enlargement.

Prognosis

- Life expectancy is typically normal with the exception of vascular EDS, which has a reduced life expectancy of ~ 50 years.

Pseudoxanthoma elasticum (PXE)

- inherited condition (**usually autosomal recessive***) connective tissue disorder involves the elastic fibres of the **eye**, **skin** and **cardiovascular** system.
  - ⇨ *there are reports of autosomal dominant inheritance in a minority of cases
- caused by mutations in the ABCC6 gene → lack of functional ABCC6 protein leads to ectopic mineralization that is most apparent in the elastic tissues of the skin, eyes and blood vessels.

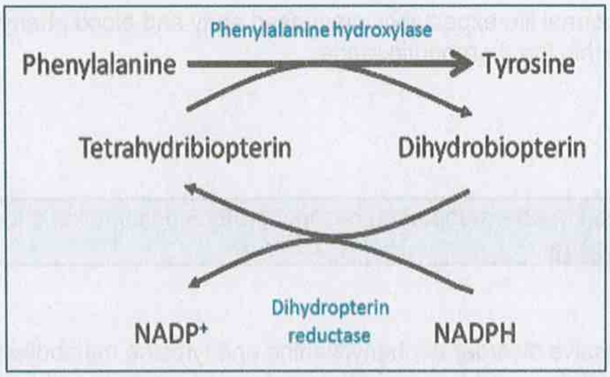
Features

- **Eye**
  - ⇨ retinal angioid streaks
    - due to dystrophic calcification of Bruch's membrane
  - ⇨ Visual loss can occur by infarction of the visual pathways and is likely to explain the chronic changes of optic disc atrophy
- **Skin**
  - ⇨ **'plucked chicken skin' appearance** - small yellow papules on the neck, antecubital fossa and axillae
    - The first clinical sign
- **Cardiac**
  - ⇨ mitral valve prolapse,
  - ⇨ increased risk of ischaemic heart disease
  - ⇨ Due to loss of elastic tissue, patients have an increased incidence of mitral regurgitation, aortic regurgitation and aortic dissection.
- **Gastrointestinal haemorrhage**
- **CNS**
  - ⇨ Cerebral ischaemia in PXE is caused by small vessel occlusive disease.
  - ⇨ Intracranial aneurysms
  - ⇨ Subarachnoid and intracerebral haemorrhages
  - ⇨ Progressive intellectual deterioration
  - ⇨ Mental disturbances, and
  - ⇨ Seizures.

Phenylketonuria (PKU)

Overview

- Autosomal recessive condition
- Caused by a disorder of phenylalanine (an essential amino acid) metabolism.
  - ⇨ usually **due to defect in phenylalanine hydroxylase**, an enzyme which converts phenylalanine to tyrosine .
  - ⇨ In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase.
- The gene for phenylalanine hydroxylase is located on chromosome 12.
- The incidence of PKU is around 1 in 10,000 live births.
- High levels of phenylalanine lead to problems such as learning difficulties and seizures.



- The sequence of phenylalanine metabolism is the following: phenylalanine → tyrosine → L-Dopa → dopamine → norepinephrine → epinephrine.
  - ⇨ **the neurological symptoms are most likely caused by a reduction in which neurotransmitters?**
    - ➔ Norepinephrine

Features

- usually presents by 6 months e.g. with developmental delay, seizures, typically infantile spasms
- child classically has fair hair and **blue** eyes
- learning difficulties. **Even with dietary treatment some degree of cognitive impairment is seen**
- Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth are found in untreated children.
- Eczema
- partial albinism due to decreased tyrosine production.
- **'musty' odour** to urine and sweat secondary to phenylacetate, a phenylketone

Diagnosis

- Diagnosis of classic PKU requires raised Phe levels, **increased urinary Phe metabolites** and normal cofactor (tetrahydrobiopterin) concentrations.
  - ⇨ plasma levels of tyrosine are difficult to measure, and have diurnal variation. Whilst the levels are often low in patients with PKU, the levels can be normal depending on what time of the day the sample is taken and whether or not the patients are being treated.
- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- hyperphenylalaninaemia
- phenylpyruvic acid in urine

Management

- **Low phenylalanine** and **high tyrosine diet**

Prognosis

- Excellent with normal life expectancy diagnosed early and blood phenylalanine (phe) levels remain within the therapeutic range.

Alkaptonuria

> The **black** discoloration of sclera and urine becoming **black** on standing should alert you to the likelihood of **Alkaptonuria**.

Pathophysiology

- Autosomal recessive disorder of phenylalanine and tyrosine metabolism
- **Caused by** a **deficiency of homogentisic acid oxidase** responsible for the degradation of homogentisic acid produced from phenylalanine and tyrosine.
- Accumulation of homogentisic acid causes pigmentation of the urine, sclera and connective tissues.
- Alkaptonuria is generally a benign and often asymptomatic condition.

Features

- Pigmented sclera
- **Urine turns black if left exposed to the air**
- Deposition in the joints causes cartilage pigmentation (ochronosis) and degeneration.
  - ⇨ **Patients develop arthritis at 40 years of age.**
  - ⇨ intervertebral disc calcification may result in back pain
  - ⇨ The knees and spine are commonly affected.
  - ⇨ The sacroiliac joint may be spared.
- Renal stones
- Homogentisic acid is a reducing agent, therefore it gives a false **positive Glucostix test** but normal Clinitest.

Treatment

- High-dose vitamin C
- Dietary restriction of phenylalanine and tyrosine

X-linked recessive

Key Characteristics

1. **Gender Differences**:
   - **Males**: A single mutated X chromosome causes the disease.
   - **Females**: Both X chromosomes must carry the mutation to exhibit the disease, which is rare.
2. **Carrier Females**:
   - Often asymptomatic but may show mild symptoms due to **X-inactivation** (lyonization).
3. **Inheritance Risk**:
   - Affected males cannot pass the disease to their sons (they pass the Y chromosome).
   - Carrier females have a **50% chance** of passing the mutation to sons (affected) and **50% chance** to daughters (carriers).

> **X-linked recessive conditions - there is no male-to-male transmission. Affected males can only have unaffected sons and carrier daughters.**

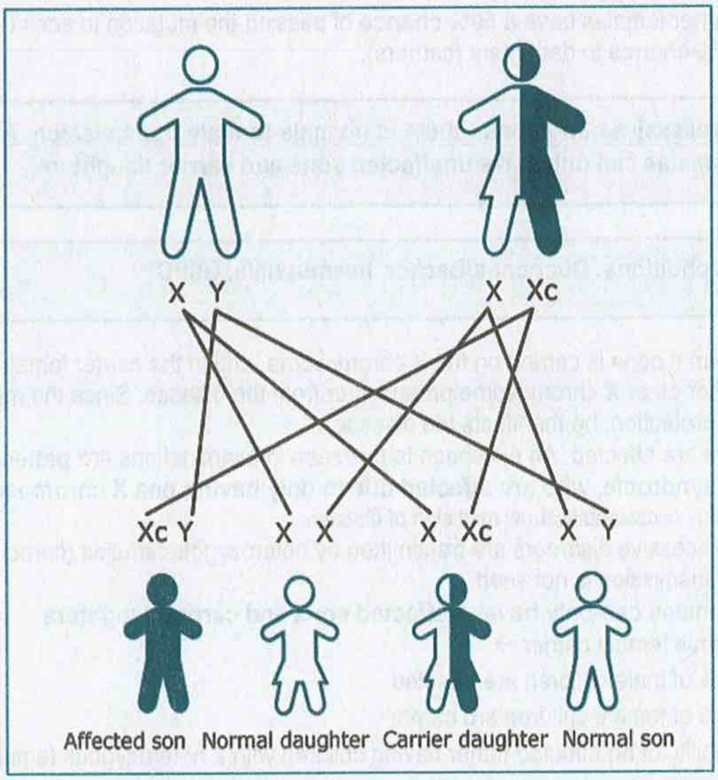
> **X-linked conditions: Duchenne/Becker, haemophilia, G6PD**

- The abnormal gene is carried on the X chromosome, and in the carrier female, the normal allele on her other X chromosome protects her from the disease. Since the male does not have this protection, he manifests the disease.
- only males are affected. An exception to this seen in examinations are **patients with Turner's syndrome, who are affected due to only having one X chromosome.**
- Females only occasionally show mild sign of disease
- X-linked recessive disorders are transmitted by heterozygote females (carriers) and male-to-male transmission is not seen.
- **Affected males can only have unaffected sons and carrier daughters.**
- heterozygous female carrier →
  - 50% of male children are affected
  - 50% of female children are carrier
- The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.
- **Many of the inherited eye disorders such as retinitis pigmentosa and ocular albinism are inherited in an x-linked recessive pattern.**

- **The following conditions are inherited in a X-linked recessive fashion:**

⇨ Androgen insensitivity syndrome	⇨ Hunter's disease
⇨ Becker muscular dystrophy	⇨ Lesch-Nyhan syndrome
⇨ Colour blindness	⇨ Nephrogenic diabetes insipidus
⇨ Duchenne muscular dystrophy	⇨ Ocular albinism
⇨ **Fabry's disease**	⇨ Retinitis pigmentosa
⇨ G6PD deficiency	⇨ Wiskott-Aldrich syndrome
⇨ **Haemophilia A,B**	⇨ Fragile X syndrome

- **The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:**
  - ⇨ Chronic granulomatous disease (in > 70%)



What is the most common genetic disorder ?

➲ **Sex-linked disorder**

- The most common genetic disorder is actually a relatively minor one, red-green colour blindness, which is seen in 2–4% of men.
- Other examples of more significant sex-linked disorders include haemophilia A and B.

X-linked dominant disorders

- **No carrier (the carrier of a defective gene associated with a disorder, will have the disorder)**
- **affected woman**
  - **→ Half of the daughters and sons are affected**
  - **→ male will have worse symptoms than female (because women carry two X)**
- **affected father → all his daughters are affected but none of his sons.**

- The gene responsible for a genetic disorder is located on the X chromosome, and only one copy of the allele is sufficient to cause the disorder when inherited from a parent who has the disorder.
- X linked dominant disorders are rare (for example, **vitamin D-resistant rickets**).
- They affect both sexes but **females more than males.**
  - ⇨ Males can only get an X chromosome from their mother whilst females get an X chromosome from both parents. As a result, females tend to show higher prevalence of X-linked dominant disorders because they have more of a chance to inherit a faulty X chromosome.
- Homozygous mother → All children are affected.
- An affected mother with the trait → half the sons and half the daughters inherit the disorder
- when the mother alone is the carrier ; she herself will have the disorder.
  - ⇨ 50% Of her daughters and sons will have the disorder,
  - ⇨ 50% will be unaffected.
- **Affected females will transmit the condition to 50% of their children, whether male or female.**
- When the father alone is the carrier of a defective gene associated with a disorder, he too will have the disorder.
  - ⇨ 100% Of his daughters will have the disorder, since all of his daughters will receive one copy of his single X chromosome.
  - ⇨ none of his sons will have the disorder; sons do not receive an X chromosome from their father.
  - ⇨ **affected father → all his daughters are affected but none of his sons.**

Vitamin D-resistant rickets

Overview

- Vitamin D-resistant rickets is a **X-linked dominant** condition
  - ⇨ affected female will transmit the disease to 50% of her sons and 50% of her daughters.
  - ⇨ affected male will transmit the condition to all of his daughters but none of his sons.
- usually presents in infancy with failure to thrive.
- **caused by impaired phosphate reabsorption in the renal tubules**

Features

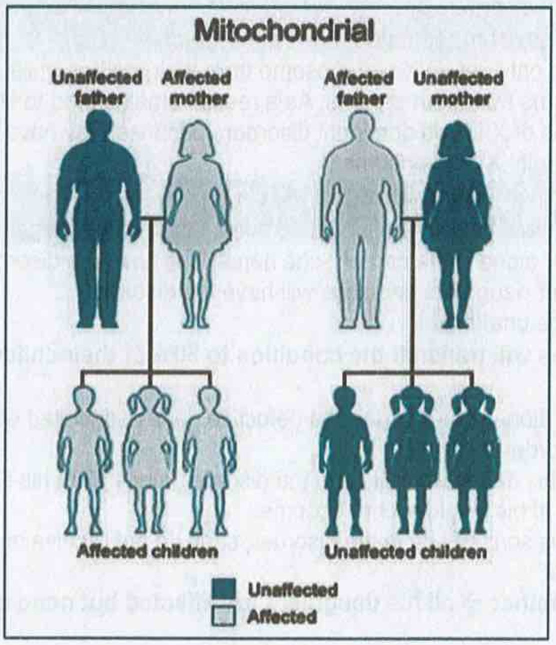
- failure to thrive
- normal serum calcium, **low phosphate**, elevated alkaline phosphotase
- x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis
- made by demonstrating **increased urinary phosphate**

Management
- high-dose vitamin D supplements
- oral phosphate supplements

Mitochondrial diseases

Mitochondrial diseases follow a maternal inheritance pattern



- Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Characteristics: Mitochondrial inheritance has the following characteristics:
- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally, encode rare neurological diseases
- **poor genotype: phenotype correlation** - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

Histology

- muscle biopsy classically shows **'red, ragged fibres'** due to increased number of mitochondria

Examples

- **Leber's optic atrophy**
  - ⇨ Cyanocobalamin (a form of B12) should be avoided as it may lead to blindness in Leber's disease patients.
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- **MERRF syndrome: myoclonus epilepsy with ragged-red fibres**
  - ⇨ generalised myoclonus (60%),
  - ⇨ epilepsy,
  - ⇨ optic atrophy (20%),
  - ⇨ short stature (10%),
  - ⇨ ataxia,
  - ⇨ cognitive decline
  - ⇨ encephalopathy (EEG findings of generalised slow waves)
  - ⇨ sensorineural hearing loss
  - ⇨ impaired glucose tolerance.
- sensorineural hearing loss

Myoclonic epilepsy with ragged red fibres (MERRF)
A young patient presenting with cognitive impairment developing after a period of normal development, seizures, myoclonic jerks, Wolff-Parkinson White syndrome and worsening vision (consistent with optic atrophy).
Diagnosis → **(MERRF),** which is a mitochondrial DNA disorder **diagnosed by → ragged red fibres on muscle biopsy.**

Kearns-Sayre syndrome

Kearns-Sayre syndrome:

- **Mitochondrial inheritance**
- **Onset < 20-years-old**
- **Triad of:**
  - ⇨ **External ophthalmoplegia**
  - ⇨ **Retinitis pigmentosa and**
  - ⇨ **Heart block.**

Overview

- mitochondrial DNA mutation.
- onset in patients < 20 years old

Features

- **external ophthalmoplegia → Ptosis**
- **retinitis pigmentosa**
- **heart conduction defect**
- sensorineural hearing loss is almost universal in those who survive into the fourth decade of life; this may not be fully corrected with hearing aids.
- Other associated features:
  - ⇨ cerebellar ataxia,
  - ⇨ raised cerebrospinal fluid (CSF) proteins,
  - ⇨ proximal myopathy.
  - ⇨ short stature
  - ⇨ **multiple endocrinopathies** including diabetes mellitus, hypoparathyroidism, and Addison disease.

Diagnosis

- **Muscle biopsy may reveal ragged red fibers.**
- Muscle histochemistry reveals **deficiency of cytochrome c oxidase** (mitochondrial respiratory chain enzyme).

Prognosis

- Patients rarely live beyond their 40s and there are no therapeutics currently available.

Kallman's syndrome

Kallman's – LH & FSH low – normal

Klinefelter's – LH & FSH – raised

Overview

- Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism.
- It is usually inherited as an **X-linked recessive** trait.
- Caused by failure of GnRH-secreting neurons to migrate to the hypothalamus → gonadotrophin releasing hormone (GnRH) deficiency
- May arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF-1).
- There is isolated gonadotrophic deficiency (may be evidenced by a normal prolactin).
- The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Incidence

- 1 in 10,000 males
- More common in men: male to female ratio of 4:1.

Features

- **Hypogonadotrophic hypogonadism**
  - ⇨ Sex hormone levels are low
  - ⇨ LH, FSH levels are inappropriately low/normal
  - ⇨ Lack of development of secondary sexual characteristics
  - ⇨ Primary amenorrhoea.
- **Infertility**
  - ⇨ In male individuals: cryptorchidism and low sperm count
  - ⇨ In female individuals: primary amenorrhea
- **Cryptorchidism (Cryptorchidism is more suggestive of Kallman's than Klinefelter's syndrome)**
  - ⇨ Cryptorchidism is the absence of one or both testes from the scrotum (undescended testis).
- **Anosmia** present in 75% **(Lack sense of smell) due to failure of the olfactory bulb to develop, leading to loss of gonadotropin releasing hormones.**
- Patients are typically of normal or above average height
- **No mental retardation**
- **Delayed puberty:** (e.g., absent thelarche in female individuals, decreased growth spurt)
- Associated disorders
  - ⇨ Renal agenesis
  - ⇨ Cleft lip/cleft palate
  - ⇨ Visual defects : colour blindness
  - ⇨ Deafness

Diagnosis

- **Diagnostic test → Fluorescent in situ hybridisation (FISH) is currently the best means of a genetic diagnosis**
- Absent olfactory bulbs are present on 75% of MRI scans in these patients.
  - ⇨ **The appearance on cerebral MRI → Absent olfactory bulbs**

Treatment

- **For a male who begin a relationship with a woman**
  - ⇨ **Pulsed (NOT Continuous) GnRH treatment** is needed to restore LH and FSH release.
    - It needs to be continued for as long as fertility is required.
    - As natural GnRH release is pulsatile, continuous therapy fails to lead to LH and FSH release.
    - Once his family is complete, switching to testosterone therapy may be more convenient for him.
    - Although Testosterone supplementation will restores secondary sexual characteristics, it doesn't restore fertility and is therefore not appropriate here.
    - FSH can be used to induce fertility, but it is less effective than pulsed GnRH therapy.
- **If fertility is not required**, there is no need to stimulate spermatogenesis with (GnRH) or gonadotropins; **only testosterone** replacement is required.

- LH can be used in conjunction with FSH **to induce fertility in women with Kallmann syndrome**.
- **For a woman who wants to start a family:**
  - ⇨ **HCG** to drive production of gonadal steroid hormones, **FSH** to drive ovulation, harvesting of eggs, and **IVF**. This process is most effective in achieving successful pregnancy.

Klinefelter's syndrome

Klinefelter's? - do a karyotype

Overview

- Klinefelter's syndrome is associated with male phenotype and **47, XXY karyotype**
- the commonest form of which is XXY, is the result of chromosomal non-dysjunction; as such, it does not follow a mendelian pattern of inheritance.
- it is the most common chromosomal disorder associated with male hypogonadism and infertility.
- Incidence: between **1 in 500** and 1 in 1000.
- The rate of chromosomal non-dysjunction increases with increasing maternal age and increasing paternal age, each parent contributing 50% of the risk. Around 60% of Klinefelter cases do not survive the fetal period.
- **has no specific genetic pattern of inheritance**
  - ⇨ **chances of inheriting the disorder → < 1%**

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile, azoospermia
- gynaecomastia
  - ⇨ **increased incidence of breast cancer** (20 times higher than a normal male).
- elevated gonadotrophin levels **(↑↑LH/FSH)** due to testicular failure
  - ⇨ Leydig cell dysfunction → ↓ testosterone → ↑ LH → ↑ estrogen.
  - ⇨ dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH.
- Low testosterone levels
- **Low HDL cholesterol**, elevated triglyceride ,normal or increased (LDL)
- increased cardiovascular risk due to lipid abnormality.
- decrease libido
- decrease bone mineral density → increased risk of osteoporotic fractures.

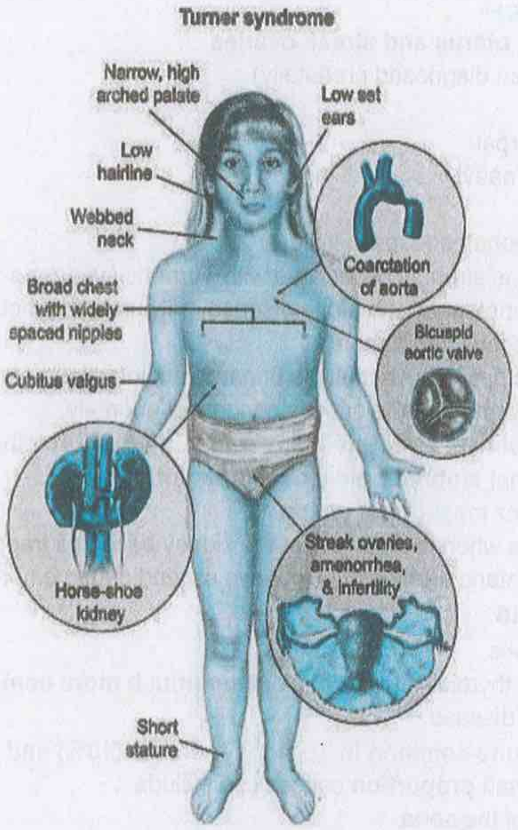
Investigation

- **Diagnosis is by chromosomal analysis**
- **the most appropriate investigation in suspected cases → FSH, LH**
  - ⇨ Both FSH and LH are raised in Klinefelter syndrome, and elevation would be a strong pointer to confirming the underlying diagnosis.
  - ⇨ more useful than Testosterone (wouldn't indicate whether the defect was at the level of the pituitary or the testes)

Treatment → Testosterone

- **Testosterone is known to improve bone mineralization and is the treatment of choice**

Turner's syndrome



Turner's syndrome - most common cardiac defect is bicuspid aortic valve

Overview

- affects around 1 in 2,500 females.
- caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes.
- **denoted as 45,XO or 45,X**

Features

- short stature
- shield chest, widely spaced nipples
- webbed neck
- cardiac defects:
  - ⇨ **bicuspid aortic valve (15%),**
  - ⇨ coarctation of the aorta (5-10%)
    - hypertension and systolic murmur
- **primary amenorrhoea**
- **associated absent uterus and streak ovaries**
- cystic hygroma (often diagnosed prenatally)
- high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- **keloid scars**
- lymphoedema in neonates (especially feet)
- **Horseshoe kidney** is strongly associated with Turner's syndrome
  - ⇨ often initially presents with stone disease, pelviureteric junction (PUJ) obstruction, trauma, infections and tumors.
  - ⇨ In a pediatric patient with multiple urinary tract infections or renal stones, imaging must be performed to rule out this congenital anomaly.
  - ⇨ **Which anatomical structures is responsible for horseshoe kidney anomaly during normal embryological development?**
    - **Inferior mesenteric artery**
    - occurs when the isthmus of the kidney becomes trapped behind the inferior mesenteric artery as the kidneys ascend during embryonic life.

Associated conditions

- autoimmune diseases:
  - ⇨ autoimmune thyroiditis **(hypothyroidism (much more common in Turner's))**
  - ⇨ and Crohn's disease
- **Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic - essential.** In a **small proportion** causes can include:
  - ⇨ coarctation of the aorta
  - ⇨ and renal dysfunction due to horsehoe kidney.
- metabolic abnormalities (dyslipidaemia and glucose intolerance)
- recurrent otitis media.
- Diabetes mellites
  - ⇨ Although the incidence of diabetes mellitus is increased in patients with Turner syndrome, it is thought to be driven by insulin resistance and is very responsive to weight loss.

Diagnosis
- karyotype → **identification of 45X0 .**

Prognosis
- **What condition is responsible for most of the excess mortality associated with Turner syndrome?**
  - ⇨ Thoracic aortic aneurysm rupture

Marfan's syndrome

Marfan's syndrome is caused by a mutation in a protein called fibrillin-1

Overview
- **autosomal dominant** connective tissue disorder.
- caused by a defect in the fibrillin-1 gene on chromosome **15**
  - ⇨ Mutation of **FBN1** that encodes **Fibrillin-1**.
- affects around 1 in 3,000 people.
- may occur as a spontaneous mutation, (1/3rd of cases), and this occurs more commonly to offspring of older males.

Features
- Skeletal
  - ⇨ tall stature with arm span to height ratio > 1.05
  - ⇨ high-arched palate
  - ⇨ arachnodactyly
  - ⇨ pectus excavatum
  - ⇨ pes planus
  - ⇨ scoliosis of > 20 degrees
  - ⇨ crowded teeth.
  - ⇨ Dural ectasia:
    - ballooning of the dural sac at the lumbosacral level
    - Dural ectasia affects around 60% of patients with Marfan's syndrome.
    - **It may cause lower back pain associated with neurological problems such as bladder and bowel dysfunction.**
  - ⇨ **ligamentous/joint laxity resulting in multiple joint dislocations,** hypermobile joints
- **Heart:**
  - ⇨ **Dilation of the aortic sinuses (seen in 90%)** which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%).
- Lungs: repeated pneumothoraxes
- Eyes:
  - ⇨ **Upwards** lens dislocation (superotemporal ectopia lentis) seen in 50% of patients
  - ⇨ **Retinal detachment**
  - ⇨ Blue sclera, myopia, early glaucoma, and early cataracts.

Diagnosis

- Unfortunately, **DNA testing for fibrillin gene mutations, whilst helpful, cannot exclude a diagnosis of Marfan because a number of mutations exist (at least 130)**.
- Hence **diagnosis is made on the major and minor features associated with the syndrome.**

Prognosis & treatment:

- The life expectancy of patients used to be around 40-50 years.
- With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.
  - ⇨ Treatment with **β-blockers** reduces the rate of aortic dilatation and the risk of rupture
- Aortic dissection and other cardiovascular problems remain the leading cause of death however.
- Pregnancy is associated with increased risk of aortic rupture.

A mutation of which gene is most closely associated with Marfan's syndrome?
➔ FBN-1 mutation
- FBN-1 gene mutation → Defect in fibrillin → Marfan's

Homocystinuria

Marfanoid skeletal abnormalities (tall and thin, elongated limbs, arachnodactyly) + mental retardation ➔ Homocystinuria

Overview

- **Autosomal recessive** disease
- Caused by **deficiency of cystathionine beta synthase** results in an accumulation of homocysteine
  - ⇨ cystathionine beta synthase is responsible for converting homocysteine to cystathionine. Cystathionine is later converted to cysteine,
    - so, patients who have this enzyme deficiency **need to supplement their diets with exogenous cysteine**.
    - Levels of homocysteine and methionine accumulate

Types

- **Homocystinuria type 1 → a defect in cystathionine synthetase is responsible.**
- Homocystinuria type 2 → defects in methylene tetrahydrofolate reductase
  - ⇨ However, individuals with this condition rarely survive the neonatal period or, if they survive longer than this, they often have more severe mental retardation.

Features

- fine, fair hair
- musculoskeletal: may be similar to Marfan's - arachnodactyly etc
- neurological: learning difficulties, mild to moderate mental handicap ,seizures
- ocular: downwards (inferonasal) dislocation of lens
  - ⇨ The sudden visual deterioration could either be due to a thrombotic episode or to the lens dislocation associated with this condition.
- **increased risk of arterial and venous thromboembolism** (atherosclerosis, thrombosis, MI)
  - ⇨ the most common cause of death.
- malar flush,
- **livedo reticularis**

Diagnosis

- made by the **cyanide-nitroprusside test**, which is also positive in cystinuria
  - ⇨ addition of sodium nitroprusside to urine → urine changes color to an intense red
- Guthrie test is used for screening the neonates for the presence of homocystinuria.

Treatment

- Dietary modification aim to: reduce intake of methionine and increase intake of cysteine.
- vitamin B6 (pyridoxine) supplements
  - ⇨ 50% of patients respond to large doses of pyridoxine (vitamin B_6)
- Folate and vitamin B12 supplements
  - ⇨ facilitate the conversion of homocysteine to methionine.
  - ⇨ homocysteine levels (homocysteinemia) are more commonly tested in diagnosis of Vitamin B12 Deficiency.

Homocystinuria VS Marfan's

	homocystinuria	Marfan's syndrome
inheritance	autosomal **recessive**	autosomal **dominant**
lens dislocation	**downward** lens dislocation	**upward** lens dislocation
aortic incompetence	heart rarely affected	aortic incompetence may occur
intellectual development	**mental retardation** (nearly 50%)	**normal**
livedo reticularis	**seen** due to the venous thrombosis in the small vessels of the skin	**NO**
other principle features	**osteoporosis**, recurrent thromboembolism; **characteristic laboratory features**: plasma methionine and homocystine levels are elevated, homocystine is excreted in the urine, plasma cystine levels are reduced, positive urine cyanide-nitroprusside test; response to treatment with pyridoxine	flat feet, herniae, scoliosis; there is a 50% reduction in life expectancy

Fragile X syndrome

Overview

- Fragile X syndrome is a disorder affecting the methylation and expression of the fragile X mental retardation 1 gene.
- genetic inheritance → X-linked dominant with variable penetration
- Patients affected by fragile X syndrome usually have over 200 **CGG** trinucleotide repeats.

Features

- moderate to severe mental retardation
- prognathism
- face: (**long** face, **prominent** forehead, **large** jaw (prognathism) and **large** ears
- macro-orchidism
    - ⇨ **In post pubertal males, abnormally large testes are a distinctive feature.**
- speech delays
- double-jointedness
- autistic symptoms,
- occasional self-mutilation.
- Otitis media, strabismus, and dental problems may be present
- hyperextensible joints
- hypotonia,
- heart problems, including mitral valve prolapse.

Management

- Treatment focused on preventing common medical problems such as gastroesophageal reflux, sinusitis, and otitis media,+
- speech, occupational, and physical therapy.

Trinucleotide repeat disorders

Anticipation in trinucleotide repeat disorders = earlier onset in successive generations

Definition

- Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides.
- These expansions are unstable and may enlarge which may lead to **an earlier age of onset in successive generations - a phenomenon known as anticipation.** In most cases, an increase in the severity of symptoms is also noted
- **Friedreich's ataxia is unusual in not demonstrating anticipation**

Examples (note dominance of neurological disorders):

- Fragile X (CGG)
- **Huntington's (CAG)**
- myotonic dystrophy (CTG)
  - ➪ CTG repeats in the DMPK gene
- Friedreich's ataxia* (GAA)
  - ➪ (*Friedreich's ataxia is unusual in not demonstrating anticipation)
- spinocerebellar ataxia
- spinobulbar muscular atrophy
- Kennedy disease, also known as 'X-linked bulbospinal neuronopathy'
- dentatorubral pallidoluysian atrophy

> **Trinucleotide repeat disorders mnemonic:**
>
> **Try (trinucleotide) hunting for my fried eggs (X).**

Genetic anticipation

> **Anticipation: successive generations present with symptoms at an earlier age**

- **Definition:** The 'classic' definition of anticipation is earlier onset in successive generations. However, in most cases, an increase in the severity of symptoms is also noted. If both options (earlier onset and sever symptoms) are presented, then the earlier onset should be chosen
- **Example:** A man **aged 33** presents with features of Huntington's disease (depression, weight loss and choreiform movements). He informs you that his father had similar symptoms **aged 50**, his grandfather **aged 75** and both deteriorated in terms of mobility and mental state, and eventually died.
- **Occur in:**
  - ➪ Huntington's disease
  - ➪ Myotonic dystrophy
  - ➪ Fragile X syndrome

Polygenic diseases

- **Definition:**
  - ➪ genetic disorder that is caused by the **combined action of more than one gene**.
  - ➪ Because such disorders depend on the presence of several genes, they are not inherited as simply as are single-gene diseases.
- **Examples:**
  - ➪ hypertension,
  - ➪ coronary heart disease,
  - ➪ diabetes
  - ➪ **Amyotrophic lateral sclerosis (ALS)**

Lysosomal storage diseases

Definition

- Lysosomal storage diseases are a group of inherited metabolic disorders caused by a deficiency of specific enzymes. This causes an accumulation of abnormal substances that are usually degraded within lysosomes, resulting in cell damage and death.

Risk factors

- Ashkenazi ethnicity
- Male sex
  - ⇨ Fabry's disease is X-linked, but heterozygous females typically (>75%) do have symptoms, although less severe, more variable in expression, and at a later age of onset.

Key features

- Hyperacusis → Characteristic of Tay-Sachs disease.
- Optic atrophy or retinitis pigmentosa are seen in juvenile form of Tay-Sachs disease.
- hx of renal failure → Found in adult Fabry's disease.
- Hepatosplenomegaly → common in Gaucher's disease
- onset in adulthood (Fabry's, Gaucher's type 1, Pompe's)

Diagnosis

- **Enzyme assay (1st investigations to order)**

Gaucher's disease

Gaucher
- **Glucocerebrosidase deficiency**
- **Glucocerebroside accumulation**

Features involve multiple systems: Blood (pancytopaenia , anaemia, recurrent infections,) bones, hepatosplenomegaly, lung (cough) → think of Gaucher's disease

Pathophysiology

- **Autosomal recessive** mutation in the glucocerebrosidase (GBA) gene located on **chromosome 1** → **Deficiency of β-glucocerebrosidase** → **accumulation of glucocerebroside** (sphingolipid found in cell membranes that can accumulate in the lysosome of macrophages) in the brain, liver, spleen, and bone marrow (i.e., Gaucher cells).

Epidemiology

- Gaucher's disease is the most common lysosomal storage diseases.
- About one in 100 people in the United States are carriers of the most common type of Gaucher disease (**type I**).
- The carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is one in 450.

Consequences

- **Parkinson's disease is more common in Gaucher's disease patients (**the most commonly known genetic risk factor for Parkinson's**)**
- Cancer risk may be increased, particularly myeloma.

Types

- **GD type I (Chronic non-neuropathic; adult** Gaucher disease)
  - ⇨ **Most common form**
  - ⇨ **Associated with a normal lifespan**
- GD type II (**Acute neuropathic**; **infantile** Gaucher disease)
  - ⇨ typically begins within 6 months of birth
  - ⇨ Symptoms include progressive brain damage, spasticity and seizures.
  - ⇨ carries the worst prognosis, affected children **usually die by age two.**
- GD type III (**Subacute neuropathic**; juvenile Gaucher disease)
  - ⇨ can begin at any time in childhood or even in adulthood
  - ⇨ characterized by slowly progressive, but milder neurologic symptoms compared to type II.
  - ⇨ **Patients often live into their early teen years and adulthood**

Features

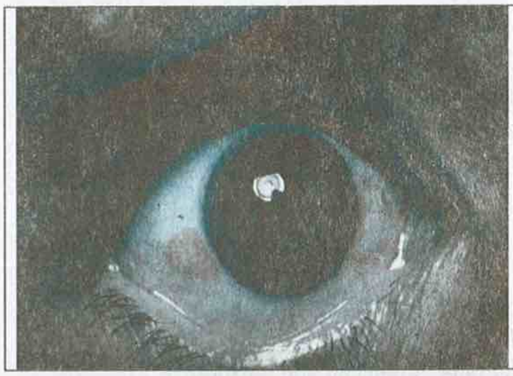
- Hepatosplenomegaly (**massive splenomegaly**)
- Bone pathology (bone crises, osteoporosis, aseptic necrosis) **the chief complaint is of bone pain in an adult.**
- Blood abnormalities: anemia, thrombocytopenia
- diffuse infiltrative pulmonary disease
- Growth delays
- Yellowish-brown skin and scleral pigmentation (**Characteristic yellow or yellow-brown papules (pingueculae) develop at the sclerocorneal junctions**).

Diagnosis

- **Enzyme analysis (Enzyme studies of blood leucocytes) → Reduced** glucocerebrosidase activity in leukocytes or fibroblasts
- Accumulation of glucocerebroside in leukocytes or fibroblasts
- Gaucher cell: lipid-rich macrophages with an enlarged cytoplasm with inclusions that resemble crumpled tissue paper on microscopy

Treatment

- Recombinant glucocerebrosidase.

	The slide shows yellow papules (pingueculae) in the cornea; these are characteristic of Gaucher disease.

Common exam questions

- **Features of anaemia, recurrent pneumonia, bone pain and hepatosplenomegaly. Which of the following is the most likely diagnosis?**
  - ⇨ **Gaucher's disease**
- **Features of anaemia, recurrent pneumonia, bone pain and hepatosplenomegaly .Which of the following is the most likely enzyme deficiency found in this patient?**
  - ⇨ **Glucocerebrosidase**

> **Gaucher disease causes massive splenomegaly**

Fabry's disease

Pathophysiology (a lysosomal storage disorder)

- X-linked recessive **mutation → α-Galactosidase A deficiency →** accumulation of trihexoside ceramide (a glycolipid found in multiple body tissues) in the endothelium of vessels, in the epithelium of many organs, and in smooth muscle cells → disorder affecting many organ systems.

Epidemiology

- Typical onset is during childhood but may also appear in 60–80-year-old adults
- Mainly affects boys

Features

- **Early features**
  - ⇨ **Peripheral neuropathy:** Periodically occurring dysesthesia in the hands and feet caused by small fiber neuropathy , which manifests as burning pain (Fabry crises)
  - ⇨ Anhidrosis or hypohidrosis (decreased sweating)
  - ⇨ Angiokeratomas (warty skin lesions with telangiectasia and hyperkeratinized covering)
  - ⇨ Corneal clouding
  - ⇨ Cataract

- **Late features**
  - ⇨ Restrictive cardiomyopathy
  - ⇨ Cerebrovascular lesions (TIA and stroke)
  - ⇨ Fabry nephropathy, causing progressive renal failure (the first manifestation of renal insufficiency in Fabry disease is proteinuria.)

The disorder has three distinct clinical entities:

1. Classical presentation in the male homozygote with early presentation in childhood - angiokeratomas, heart failure, cataracts and renal disease
2. **Male homozygotes with atypical presentation in adulthood with proteinuria, acroparaesthesia, angiokeratomas and cardiomegaly**
3. Female heterozygotes can present again in adulthood with similar mild symptoms.
   - An X linked recessively inherited condition can exist in female carriers who may exhibit mild to moderate symptoms. This is due to variable expression according to random X inactivation of the affected gene in embryogenesis

most common symptoms → peripheral neuropathy, angiokeratomas, and hypohidrosis.

Diagnosis

- **Absent or deficient levels of alpha-galactosidase A** in leucocytes, plasma or cultured fibroblasts.
- Gene analysis of alpha-galactosidase A (GLA) gene (the gold standard for the diagnosis)
- Slit-lamp examination of the cornea → microscopic lipid deposits
- Microscopy of the spun urine sediment may demonstrate 'Maltese cross' lipid globules

In Fabry d'sease, tissue accumulation of which is most likely to occur?
➧ Trihexosyl ceramide

Treatment

- Enzyme replacement therapy with α-galactosidase A

Mucopolysaccharidoses (MPS) (Hurler's & Hunter's syndromes)

Pathophysiology

- Mutations in lysosomal enzymes → impaired breakdown of glycosaminoglycans → Accumulation of glycosaminoglycans, i.e., heparan sulfate (HS) and dermatan sulfate (DS)

Features

- Occur in both conditions (typically milder in Hunter syndrome):
  - ⇨ Developmental delay
  - ⇨ Facial dysmorphism: frontal bossing, elongated skull , flattened nasal bridge, broad nasal tip, thickened gingiva, anteverted nostrils, constant nasal discharge, spaced and protruded eyes.
  - ⇨ Airway obstruction
  - ⇨ Hepatosplenomegaly

Diagnosis

- Increased urinary levels of dermatan sulfate (DS) and heparan sulfate (HS)
- Enzyme assay to confirm specific enzyme deficiency (definitive test)

Treatment

- Enzyme replacement therapy
- Bone marrow transplantation

	Hurler syndrome (mucopolysaccharidosis type I)	Hunter syndrome (mucopolysaccharidosis type II)
Inheritance	Autosomal recessive	X-linked recessive
Pathophysiology	Deficiency of α-L-iduronidase (enzyme responsible for the hydrolysis of glycosaminoglycans)	Deficiency of iduronate-2-sulfatase
Features	➲ **Corneal clouding** ➲ Inguinal hernia	➲ Aggressive behavior, Hyperactivity ➲ **No corneal clouding** ➲ Carpal tunnel syndrome

Which feature suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome?
➔ Cloudy cornea.

Hunter syndrome presents as Hurler syndrome, but patients with Hunter syndrome have normal vision and <u>aggressive</u> behavior.

<u>Glycogen storage disorders (GSD)</u>

Key feature of glycogen storage disorders:

- Tay-Sachs commonly has a 'cherry red spot' macula
- Pompe disease leads to cardiomyopathies
- McArdle's disease leads to rhabdomyolysis after exercise and lactic acidaemia
- Von Gierke disease leads to hypoglycaemia and hepatomegaly

Pompe trashes the Pump (heart)

Glycogen

- Glycogen is the storage form of carbohydrate, found predominantly in muscle and liver.
- **Chains of glucose residues are linked by alpha-1,4 glycosidic bonds, i.e. between the first carbon of one glucose and the fourth carbon of the next. Branches occur about every ten residues, and are formed by alpha-1,6 glycosidic linkages.**
- Glycogen synthesis and degradation occur at the tips of branches, with the branching structure increasing the number of sites at which glucose residues can be added or removed.

> Pompe's disease or acid maltase deficiency **(glycogen storage disorder type 2): is a deficiency in alpha-glucosidase.** It produces a myopathy , restrictive cardiomyopathy and hepatomegaly.

> **Glycogen storage disorders:**
> - **Muscle involvement (muscle glycogenoses): Types II, III, IV, V**
> - **Liver involvement (liver glycogenoses): Types I, III, IV**
> - **Types III and IV (late-onset type) may present with both muscle and liver involvement**
> - **NO liver involvement → V**

- Autosomal recessive
- All types of glycogen storage diseases result in abnormal metabolism and product accumulation within cells.
- Type IV (Andersen's disease) is the only one **GSD** involved in Glycogen Synthesis. The rest are involved in Glycogen degradation.

Diagnosis

- **Periodic acid-Schiff stain is helpful in diagnosing glycogen storage disorders.**

Type I (Von Gierke's disease)

- Relative frequency: ~25%
- Deficient enzyme
  - ⇨ **Type 1a** → Glucose-6-phosphatase
    - Role of the enzyme → Hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate
  - ⇨ **Type 1b** → Glucose-6-phosphate translocase
    - Role of the enzyme → Transport of glucose-6-phosphate into the endoplasmic reticulum where it is hydrolyzed by glucose-6-phosphatase
- Characteristic features
  - ⇨ Hepatomegaly
  - ⇨ Severe fasting hypoglycemia, mild ketosis
  - ⇨ Severe hyperlipidemia → doll-like facies
  - ⇨ Hyperuricemia
  - ⇨ Lactic acidosis
  - ⇨ Anemia
  - ⇨ Failure to thrive

Type II (Pompe's disease)

- Relative frequency: ~15%
- Deficient enzyme: Lysosomal acid maltase deficiency
- Role of the enzyme: Glycogenolysis within the lysosome
- Characteristic features
  - ⇨ Hypertrophic cardiomyopathy and/or conduction blocks
  - ⇨ Proximal myopathy
  - ⇨ Macroglossia
  - ⇨ Failure to thrive

Type III (Cori's disease)

- Relative frequency: ~25%
- Deficient enzyme: debranching enzyme (alpha-1,6-glucosidase).
- Role of the enzyme: Glycogenolysis
- Characteristic features
  - ⇨ Generalized muscle weakness and/or cramps
  - ⇨ Hepatomegaly
  - ⇨ Possibly cirrhosis (ascitis, splenomegaly)
  - ⇨ Mild, fasting hypoglycemia and ketosis
  - ⇨ Hyperlipidemia

Type IV (Andersen's disease)

- Relative frequency: ~3%
- Deficient enzyme: **Glycogen branching enzyme**
- Role of the enzyme: **Glycogenesis**
- Characteristic features
  - ⇨ Proximal myopathy
  - ⇨ Hepatomegaly
  - ⇨ Possibly cirrhosis (ascites, splenomegaly)

Type V (McArdle's disease)

- Relative frequency: ~2%
- Deficient enzyme: Muscle phosphorylase (myophosphorylase)
- Role of the enzyme: Glycogenolysis
- Characteristic features
  - ⇨ Generalized muscle weakness, exercise intolerance (with a second wind phenomenon) ,
  - ⇨ Rhabdomyolysis and myoglobinuria

Collagen Types

Types of collagen		
	Tissue distribution	**Related conditions**
Type I collagen (90% of body collagen)	Bone (produced by osteoblasts), skin, tendons, ligaments, fascia, dentin, cornea, internal organs, scar tissue (late stages of wound healing)	Osteogenesis imperfecta type I: decreased production
Type II collagen	Cartilage (including hyaline), vitreous humor of the eye, intervertebral discs (nucleus pulposus)	Achondrogenesis (type II)
Type III collagen (reticulin)	Reticular fibers in skin, blood vessels, granulation tissue, uterus, scar tissue (early stages of wound healing), fetal tissue in early embryos and throughout embryogenesis	Ehlers-Danlos syndrome (vascular type): decreased production
Type IV collagen	Basement membranes, lens	Alport syndrome: decreased production Goodpasture syndrome: autoantibodies target type IV collagen
Type V collagen	Bone, skin, fetal tissue, placenta	Ehlers-Danlos syndrome (classic type)

Collagen Diseases

Collagen diseases involve abnormalities in collagen production, structure, or function, leading to various connective tissue disorders. Collagen is a key protein that provides structural integrity to skin, bones, blood vessels, and other tissues.

Common Collagen Diseases

Disease	Type of Collagen Affected	Key Features
Osteogenesis Imperfecta	Type I	- Brittle bones, frequent fractures. - Blue sclera. - Hearing loss. - Dentinogenesis imperfecta.
Ehlers-Danlos Syndrome (EDS)	Types I, III, and V	- Hypermobile joints. - Fragile, stretchy skin. - Easy bruising. - Vascular type (Type III): arterial rupture.
Alport Syndrome	Type IV	- Progressive kidney disease (hematuria, proteinuria). - Sensorineural hearing loss. - Ocular abnormalities.
Goodpasture Syndrome	Type IV	- Autoimmune attack on basement membrane of kidneys and lungs. - Hematuria, pulmonary hemorrhage.
Marfan Syndrome	Not collagen (fibrillin-1 defect)	- Skeletal abnormalities (long limbs, scoliosis). - Aortic root dilation, mitral valve prolapse. - Lens dislocation.
Systemic Sclerosis (Scleroderma)	Increased collagen production	- Skin thickening (fibrosis). - Raynaud phenomenon. - Organ involvement (lungs, heart, kidneys).
Scurvy	Type I	- Vitamin C deficiency → defective collagen synthesis. - Bleeding gums, poor wound healing. - Perifollicular hemorrhages.
Dystrophic Epidermolysis Bullosa	Type VII	- Fragile skin with blistering. - Mutation in collagen anchoring fibrils.

Pathophysiology

1. **Genetic Mutations**:
   - Affect collagen synthesis, assembly, or stability (e.g., EDS, osteogenesis imperfecta).
2. **Autoimmune Disorders**:
   - Target collagen or collagen-associated proteins (e.g., Goodpasture syndrome, systemic sclerosis).
3. **Nutritional Deficiency**:
   - Vitamin C deficiency → impaired collagen hydroxylation (e.g., scurvy).

Clinical Features

- **Skin**: Fragility, hyperextensibility, poor wound healing.
- **Joints**: Hypermobility, subluxations, arthritis.
- **Bones**: Fragility, deformities, fractures.
- **Blood Vessels**: Aneurysms, rupture, easy bruising.
- **Organs**: Fibrosis, organ failure in severe cases.

Mechanism
- poorly understood but does **involve DNA methylation**.
- Disease may occur as a result of a defect in one allele if the other allele is imprinted and hence not expressed.

Examples
- diseases involving genomic imprinting include:
  - ⇨ **P**rader–Willi syndrome (**p**aternally imprinted)
  - ⇨ Angelman syndrome (maternally imprinted)

Prader-Willi syndrome

Deletion of chromosome 15
- **Prader-Willi – paternal**
- **Angelman syndrome - maternal**

Overview
- Prader-Willi syndrome is an example of **genetic imprinting** where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:
  - ⇨ Prader-Willi syndrome if gene deleted from father
  - ⇨ Angelman syndrome if gene deleted from mother
- Prader-Willi syndrome is associated with the absence of the active **Prader-Willi gene on the long arm of chromosome 15** , this may be due to:
  - ⇨ **Microdeletion of paternal 15q11-13 (70% of cases)**
  - ⇨ Maternal uniparental disomy of chromosome 15
- **The mode of inheritance is → Non-Mendelian**

Features
- **Hypotonia during infancy**
- Dysmorphic features
- **Short stature** (Growth hormone deficiency)
- **Hypogonadism and infertility**
  - ⇨ **(risk factor for osteoporosis)**
- **Cryptorchidism** (undescended testis)
- **Learning difficulties**
- **Childhood obesity due to Hyperphagia** (abnormally desire for food → overeating → obesity)
- Behavioural problems in adolescence
- Associated with elevated ghrelin
  - ⇨ Ghrelin is a hormone produced in the fundus of the stomach and in the pancreas
  - ⇨ Ghrelin levels increase before meals and decrease afterwards
  - ⇨ Receptors for ghrelin are found in the arcuate nucleus and the hypothalamus

Treatment
- **Administration of growth hormone and sex hormones (testosterone) is the treatment of choice**
- **Calorie restriction**

MRCPUK-part-1-September 2017 exam: Which one of the following is the most common genetic cause of Prader-Willi syndrome?
➔ Microdeletion of the paternal 15q11-13

Chromosome 15 is implicated in Prader-Willi, Angelman, and Marfan syndromes.

Angelman syndrome

Overview

- Angelman syndrome is a genetic condition characterized by a mutation on the **maternal copy** of **chromosome 15**.
- occurs as a result of a phenomena known as genomic **imprinting**.
- The imprinted copy of the gene is silenced through methylation or histone modification.
- Normally, certain paternal alleles on chromosome 15 are silenced and only the maternal alleles are expressed. However, in Angelman syndrome, the maternal alleles are mutated. Hence, the patient will have disease since only the mutated maternal alleles are active.

Features

- Developmental delay
- Intellectual disability
- **Seizures, Ataxia**
- **Unprovoked laughter**
- Large mouth with tongue protrusion.
- Hypo-pigmentation with blond hair

Diagnosis

- genetic studies showing loss of function of the UBE3A gene.

Mutations

- **Missense mutation**
  - ⇨ substitution in one amino acid in a protein
  - ⇨ e.g: glutamic acid is substituted by valine in sickle-cell disease
- **Nonsense mutation**
  - ⇨ the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.
- **Insertion mutation**
  - ⇨ changes the number of DNA bases in a gene by **adding a piece of DNA**. As a result, the protein made by the gene may not function properly.
- **Frameshift mutation**
  - ⇨ insertions or deletions of nucleotides
  - ⇨ e.g: cystic fibrosis
- **Point mutation**
  - ⇨ a change in a single nucleotide
  - ⇨ e.g: C282Y mutation responsible for haemochromatosis

- **Splicing mutation**
  - ⇨ results in larger nonfunctional protein
  - ⇨ e.g: β-thalassemia
- **Large Segment Deletion**
  - ⇨ Unequal crossover at meiosis results in loss of large segment of DNA
  - ⇨ Loss of function mutation
  - ⇨ e.g., α-thalassemia (deletion of α-globin gene)
- **Termination mutation**
  - ⇨ generation of a premature stop codon
  - ⇨ e.g: Hurler syndrome

Chromosome abnormality

- Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis.

Types

- **Numerical disorders**
  - ⇨ called **aneuploidy** (an abnormal number of chromosomes), occurs when an individual either is:
    - missing a chromosome from a pair (monosomy)
      - ❖ e.g: Turner syndrome, (born with only one sex chromosome, an X).
    - has more than two chromosomes of a pair (trisomy, tetrasomy, etc.).
      - ❖ e.g: Down syndrome (trisomy 21)
  - ⇨ **Unbalanced autosomal translocation**
    - **most likely to cause a severe phenotype**
    - As a rule, the clinical effects of a chromosome abnormality reflect the amount of imbalance of genetic material. For example: all autosomal monosomies and most autosomal trisomies are incompatible with life, the exceptions being trisomy 13 (Patau syndrome), trisomy 18 (Edward syndrome) and trisomy 21 (Down syndrome); only the last of these carries a reasonable life expectancy.
  - ⇨ **Sex chromosome aneuploidy:**
    - This is associated with comparatively **less severe phenotypes**, e.g. Klinefelter syndrome (XXY) and Turner syndrome (XO).

- **Structural abnormalities:** e.g:
  - ⇨ Duplications:
    - A portion of the chromosome is duplicated, resulting in extra genetic material.
    - e.g: Charcot-Marie-Tooth disease type 1A, caused by duplication of the gene encoding peripheral myelin protein 22 (PMP22) on chromosome 17.

List of common Chromosomal disorders:

Chromosome	disorders
Chromosome 1	variegate porphyria
chromosome 3	von Hippel Lindau (VHL)
Chromosome 4	Polycystic Kidney Disease (PKD2) Huntington's disease Achondroplasia
Chromosome 6	hereditary haemochromatosis
Chromosome 7	Cystic Fibrosis
Chromosome 9	Fredrich's ataxia
Chromosome 11	Sickle Cell Disease Beta-Thalassemia
Chromosome **12**	Phenylketonuria **von Willebrand's disease**
Chromosome 13	Patau Syndrome. Wilson Disease. retinoblastoma
Chromosome 15	Marfan's Syndrome Angelman Syndrome Prader-Willi Syndrome Tay-Sachs Disease.
Chromosome 16	Polycystic Kidney Disease (PKD1) alpha- Thalassemia
Chromosome 17	Celiac Disease. Charcot-Marie-Tooth Disease. Neurofibromatosis (NF1)
Chromosome 18	Edward Syndrome
Chromosome 19	Myotonic Dystrophy
Chromosome 21	Down Syndrome
Chromosome 22	DiGeorge Syndrome. Neurofibromatosis (NF2)

McCune–Albright syndrome (MAS)

McCune-Albright syndrome:

- **Triad of patchy skin pigmentation, bone abnormalities, and endocrine abnormalities.**
- **McCune-Albright syndrome is a form of mosaicism**
- **Due to a mutation in the GNAS1 gene**

This Page Is Intentionally Left Blank

4th edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic science

Biostatistics & EBM

Updated

2022

Hypothesis

Definition:

- A hypothesis is a formal statement about the expected relationship between variables in a study. It provides a basis for statistical testing and helps guide research.

Types of Hypotheses

1. Null Hypothesis (H_0):

- **Definition:** Assumes no relationship or effect between variables.
- **Purpose:** Serves as the default or baseline assumption in statistical tests.
- **Example:** A new drug has no effect on blood pressure compared to a placebo.

2. Alternative Hypothesis (H_1):

- **Definition:** Assumes a relationship or effect exists between variables.
- **Purpose:** Represents the researcher's expectation or claim.
- **Example:** A new drug lowers blood pressure compared to a placebo.

Characteristics of a Good Hypothesis:

1. **Clear and Specific:** Clearly defines the variables and expected relationship.
2. **Testable:** Can be tested using appropriate statistical methods.
3. **Falsifiable:** Can be proven false if the data do not support it.
4. **Based on Theory:** Grounded in existing knowledge or literature.

Steps in Hypothesis Testing:

1. **State the Hypotheses:**
   - Define H_0 (e.g., no effect) and H_1 (e.g., there is an effect).
2. **Choose the Statistical Test:**
   - Depends on data type and study design (e.g., t-test, chi-square).
3. **Set a Significance Level (α\alphaα):**
   - Commonly $\alpha=0.05$ (5% chance of Type I error).
4. **Calculate the Test Statistic:**
   - Derive a numerical value (e.g., t-statistic) from the data.
5. **Compare P-Value to α\alphaα:**
   - If p-value $< \alpha$, reject H_0; otherwise, fail to reject H_0.

Key Errors in Hypothesis Testing:

1. **Type I Error (False Positive):**
   - Rejecting H_0 when it is actually true.
   - Controlled by setting α (e.g., 0.05).
2. **Type II Error (False Negative):**
   - Failing to reject H_0 when H_1 is true.
   - Influenced by sample size and study power.

Types of Errors:

Aspect	Type I Error	Type II Error
Definition	Rejecting H_0 when it is actually true.	Failing to reject H_0 when H_1 is true.
Interpretation	False positive result.	False negative result.
Cause	Data appear significant due to chance or random variation.	Insufficient evidence due to small sample size or weak effect.
Risk	Controlled by setting a significance level (α).	Related to the study's power (1 - β).
Probability	Probability of making a Type I error = α (e.g., 0.05).	Probability of making a Type II error = β (e.g., 0.20).
Impact	Concluding a treatment works when it doesn't.	Concluding a treatment doesn't work when it does.
Example	Claiming a new drug reduces mortality when it actually doesn't.	Failing to detect that a new drug reduces mortality when it actually does.

Summary of Statistical Errors

Decision	Truth	Conclusion	Error Type
Fail to reject H_0	H_0 is true	Correct (no effect or difference).	None
Reject H_0	H_0 is true	Incorrect (false positive).	**Type I Error**
Fail to reject H_0	H_1 is true	Incorrect (false negative).	**Type II Error**
Reject H_0	H_1 is true	Correct (true effect or difference).	None

Type I (Alpha) Error: "There is an effect" where in reality there is none.
Type II (Beta) Error: "There is no effect" where in reality there is one.

Practical Considerations:

- **Type I Errors: More critical in fields like drug safety (e.g., approving an ineffective or harmful drug).**
- **Type II Errors: More critical in public health (e.g., missing the effectiveness of a new vaccine).**

Power of the Test:

- **Power (1−β) is the probability of correctly rejecting H_0 when H_1 is true.**
- **Higher power reduces Type II error and is influenced by sample size, effect size, and significance level.**

Examples:

1. **Clinical Study Hypothesis:**
   - H_0: A vaccine has no effect on preventing influenza.
   - H_1: The vaccine reduces the risk of influenza.
2. **Educational Study Hypothesis:**
   - H_0: There is no difference in test scores between teaching methods.
   - H_1: One teaching method improves test scores over the other.

P-Value

Definition

- The p-value is the probability of getting the observed results (or more extreme results) if the **null hypothesis (H0H_0H0) is true**. It helps decide whether the difference or effect seen in a study is due to chance.

Example to Understand:

- Imagine you are testing a new weight loss drug.
    - **Null Hypothesis (H0H_0H0):** The drug has no effect on weight loss (it is no better than a placebo).
    - **Alternative Hypothesis (H1H_1H1):** The drug causes weight loss.
- You conduct the study and find that people taking the drug lose an average of **3kg** more than those taking the placebo. A statistical test gives you a **p-value of 0.02**.
    - **What Does the P-Value Mean?**
    - The p-value (0.02) means there is a **2% chance** of seeing this result (or a more extreme one) if the null hypothesis is true (if the drug actually does nothing).
    - Since the p-value is less than 0.05 (a common threshold), you conclude that the drug likely has a real effect and reject H_0.

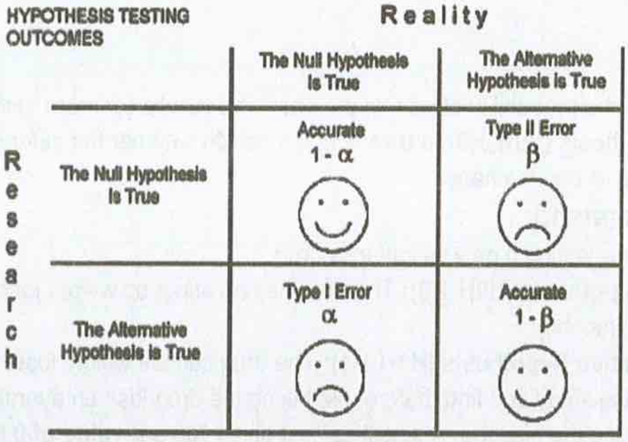
Key Takeaway:

- **Small p-value (< 0.05):** Strong evidence to reject H0H_0H0. The effect is unlikely to be due to chance.
- **Large p-value (≥ 0.05):** Insufficient evidence to reject H0H_0H0. The result could easily be due to chance.

For example:

- **P = 0.02:** Significant → The drug likely works.
- **P = 0.10:** Not significant → Cannot conclude the drug works; the result may be due to chance.

> **P-value**
> - **The p-value is the probability of obtaining the observed results or results which are more extreme if the null hypothesis is true**
> - **It is therefore equal to the chance of making a type I error**
> - **Example: if p=0.03. What does 'p=0.03' mean?**
> - **It means →** the probability that a difference between the two sample groups occurred by chance is 3%



Choosing the Appropriate Statistical Test

Key Considerations:

1. **Type of Data:**
   - **Continuous:** e.g., blood pressure, cholesterol levels.
   - **Categorical:** e.g., gender, smoking status.
   - **Ordinal:** e.g., pain scores, satisfaction levels.
2. **Objective of the Analysis:**
   - Compare groups.
   - Assess associations or relationships.
   - Evaluate predictions.
3. **Number of Groups or Variables:**
   - Two groups vs. more than two groups.
   - Independent or paired data.
4. **Data Distribution:**
   - Normal distribution → Use parametric tests.
   - Non-normal distribution or ordinal data → Use non-parametric tests.

Common Scenarios and Tests:

Objective	Data Type	Number of Groups/Variables	Statistical Test
Compare two group means	Continuous	Two independent groups	Parametric: Two-sample t-test | Non-parametric: Wilcoxon rank-sum test
Compare paired measurements	Continuous	Two paired measurements	Parametric: Paired t-test | Non-parametric: Wilcoxon signed-rank test
Compare means across groups	Continuous	Three or more independent groups	Parametric: ANOVA | Non-parametric: Kruskal-Wallis test
Test associations	Categorical	Two variables	Chi-square test
Assess correlations	Continuous	Two variables	Parametric: Pearson correlation | Non-

Objective	Data Type	Number of Groups/Variables	Statistical Test
			parametric: Spearman correlation
Predict an outcome	Continuous/Binary	Dependent and independent variables	Regression analysis (e.g., linear, logistic)

Steps to Choose a Test:

1. **Identify the objective:** Are you comparing, associating, or predicting?
2. **Determine data type:** Continuous, categorical, or ordinal.
3. **Check data distribution:** Use parametric tests for normal data; otherwise, non-parametric tests.
4. **Match test to scenario:** Select the appropriate test based on the table above.

Key Points:

- **Parametric Tests:** Require normal distribution and often used for continuous data.
- **Non-Parametric Tests:** Robust for non-normal or ordinal data.
- **Practical Tip:** Visualise data (e.g., histograms) to check for normality and guide test selection.

Comparison of Parametric vs. Non-Parametric Data

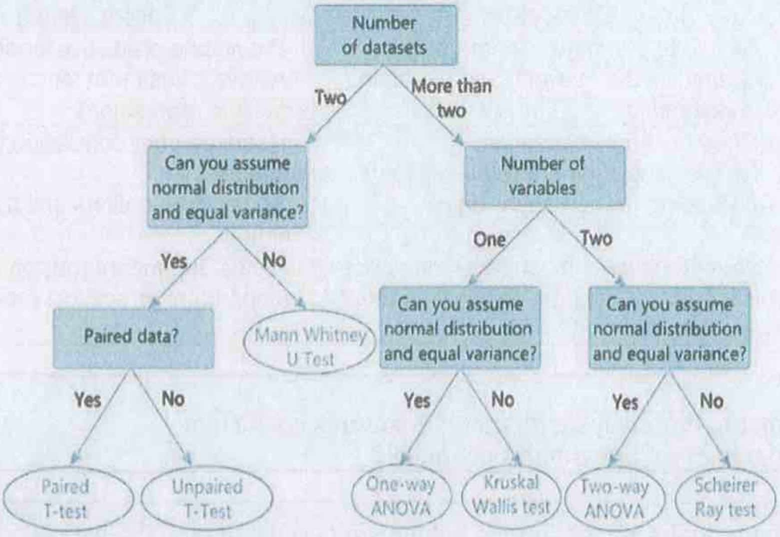
Aspect	Parametric Data	Non-Parametric Data
Definition	Data that follows a specific distribution, usually normal.	Data that does not assume any specific distribution.
Type of Data	Continuous variables (e.g., height, weight).	Ordinal, categorical, or non-normally distributed data.
Examples in Medicine	Blood pressure, cholesterol levels, BMI.	Pain scores (ordinal), satisfaction ratings, survival data.
Statistical Tests	T-tests, ANOVA, Pearson correlation, linear regression.	Wilcoxon tests, Kruskal-Wallis, Spearman correlation, log-rank test.
Strength	More powerful if assumptions are met; provides precise parameter estimates.	Robust to outliers and violations of assumptions; suitable for small samples.
Assumptions	- Data are normally distributed. - Variances are equal across groups. - Large sample size preferred.	- No assumption about the data distribution. - Applicable to skewed or ordinal data.
When to Use	Use when data are continuous, normally distributed, and assumptions hold.	Use when data are ordinal, categorical, non-normal, or assumptions are violated.

Parametric Tests

Purpose	Example	Test
Compare means between two independent groups	Compare blood pressure in treatment vs placebo groups in a clinical trial.	Two-sample t-test
Compare means of paired measurements	Measure blood pressure before and after treatment in the same group of patients.	Paired t-test
Compare means of three or more groups	Compare cholesterol levels in patients on three different drugs.	ANOVA
Assess the relationship between two variables	Determine if systolic blood pressure is related to age.	Pearson correlation
Predict a continuous outcome (variable represents a measurement or quantity, e.g Duration of hospital stay by number of days). Weight by kilograms, Cholesterol levels by mmol/L).	Assess the effect of age and BMI on drug plasma levels.	Multiple linear regression
Predict a binary outcome (a variable with only two possible categories or values, e.g Yes or No. Effective or not effective. Improved or not improved.)	Assess the likelihood of diabetes based on age and BMI.	Logistic regression

Nonparametric Tests

Purpose	Example	Test
Compare medians between two independent groups	Compare blood glucose levels in treatment vs placebo groups (non-normal data).	Wilcoxon rank-sum test
Compare medians of paired measurements	Measure improvement in pain scores before and after treatment in the same group.	Wilcoxon signed-rank test
Compare medians of three or more groups	Compare effectiveness of three therapies for chronic pain relief.	Kruskal-Wallis test
Assess the relationship between two variables	Assess the correlation between renal function and drug clearance (non-linear).	Spearman correlation
Analyse survival data with censored observations	Compare time-to-relapse for two cancer treatments.	Log-rank test
Test for association between categorical variables	Determine the relationship between smoking status (yes/no) and lung cancer (yes/no).	Chi-square test



- Categorical variables are not continuous, e.g. drug / placebo, dead / alive. They should be described as percentages or proportions and compared with a Chi-squared test.
- Normally distributed continuous data should be described as mean and standard deviation and compared with a Student's t-test.
- Skewed continuous data should be described as median and range and compared using a test such as the Wilcoxon rank-sum test or the Mann-Whitney U-test.

Correlation vs Regression

Aspect	Correlation	Regression
Definition	Measures the strength and direction of the relationship between two variables.	Predicts the value of a dependent variable based on one or more independent variables.
Purpose	To assess the association between two variables. **describes how closely two variables are associated.**	To model the relationship and predict one variable (dependent) based on another (independent).
Types	- **Pearson's Correlation Coefficient (r):** For parametric data. - **Spearman's (ρ):** For non-parametric data.	- **Simple Linear Regression:** One dependent and one independent variable. - **Multiple Regression:** One dependent and multiple independent variables. - **Logistic Regression:** For binary outcomes.
Examples	- Relationship between systolic blood pressure and age. - Correlation between smoking and lung cancer incidence.	- Predicting systolic blood pressure based on age. - Evaluating how weight and smoking predict blood sugar levels.

Aspect	Correlation	Regression
Advantage	- Simple to compute and interpret. - Quantifies the strength and direction of a relationship.	- Provides a predictive model. - Allows adjustment for confounders (multiple regression).
Limitation	- Does not imply causation. - Only evaluates linear relationships (misleading for non-linear data).	- Requires prior correlation between variables. - Sensitive to outliers and assumes linearity.
Scope	Symmetry between variables; does not distinguish dependent and independent variables.	Defines dependent (outcome) and independent (predictor) variables.

Correlation
- **parametric (normally distributed): Pearson's coefficient**
- **non-parametric: Spearman's coefficient**

In a scenario looks at whether the values are correlated, and the data is non-parametric, (e.g: pain scale), Spearman's rank correlation coefficient should be used.

Paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

MRCPUK-part-1-May-2017 exam: A study is designed to assess severity of snoring before and after using a new mandibular device. What is the most appropriate statistical test to apply to this data?
➔ Wilcoxon signed-rank test

Distribution

What is a Distribution?
- A **distribution** describes how data points are spread across a range of values.
- It shows the frequency or probability of each value in a dataset.

Key Concepts in Distribution
a. Central Tendency:
- Describes the "centre" of the data.
- **Measures:**
  - **Mean (Average):** Sum of all values divided by the number of values.
    - Sensitive to outliers (extreme values).
    - Example: Average blood pressure in a group of patients.
  - **Median:** The middle value when data is ordered.
    - Not affected by outliers.
    - Example: The median age of patients in a study.
  - **Mode:** The most frequently occurring value.
    - Useful for categorical or bimodal data.
    - Example: Most common blood type in a population.

b. Variability (Spread):

- Describes how much the data vary around the central value.
- **Measures:**
  - **Range:** Difference between the maximum and minimum values.
    - Example: Range of blood sugar levels in diabetic patients.
  - **Standard Deviation (SD):** Average distance of each data point from the mean.
    - A smaller SD means data are closer to the mean; a larger SD means more spread.
    - Example: SD of systolic blood pressure indicates variability in patient readings.

Types of Distributions

a. Normal Distribution:

- Symmetrical, bell-shaped curve.
- Most values cluster around the mean.
- **Key Features:**
  - Mean = Median = Mode.
  - Follows the **68-95-99.7 Rule:**
    - 68% of data within ±1 SD.
    - 95% within ±2 SD.
    - 99.7% within ±3 SD.
- **Example:** Heights of adults in a population.

b. Skewed Distributions:

- Data are asymmetrically spread.
  - **Right-Skewed (Positive):**
    - Tail extends to the right.
    - Mean > Median > Mode.
    - Example: Income distribution in a population.
  - **Left-Skewed (Negative):**
    - Tail extends to the left.
    - Mean < Median < Mode.
    - Example: Age at retirement in healthcare workers.

c. Bimodal Distribution:

- Two peaks in the data, indicating two subgroups.
- **Example:** Heart rates in a mixed population of adults and children.

d. Uniform Distribution:

- Data are evenly distributed across values (flat curve).
- **Example:** Equal probability of rolling any number on a fair die.

How to Identify the Distribution

- Use **visualisation tools**:
  - Histograms.
  - Boxplots.
- Calculate descriptive statistics (mean, median, mode, SD).

Implications of Distribution for Statistical Analysis

a. Normal Distribution:

- Suitable for **parametric tests** (e.g., t-tests, ANOVA).
- Assumes data are normally distributed and have equal variances.

b. Non-Normal Distribution:

- Requires **non-parametric tests** (e.g., Wilcoxon, Kruskal-Wallis).
- Robust for skewed or ordinal data.

Normal distribution vs Non-normal distribution

Aspect	Normal Distribution	Non-Normal Distribution
Shape	Symmetrical, bell-shaped	Skewed, bimodal, or uniform
Mean, Median, Mode	Mean = Median = Mode	Differ (e.g., mean > median in right-skewed)
Spread	Measured by SD (68-95-99.7 rule)	Variable; often described by range or ranks
Statistical Tests	Parametric (t-tests, ANOVA, regression)	Non-parametric (Wilcoxon, Kruskal-Wallis)

Key Takeaways

1. Central tendency and variability describe the main characteristics of data.
2. Normal distributions are symmetric and ideal for parametric analysis.
3. Non-normal distributions, including skewed and bimodal, require specialised non-parametric tests.
4. Visualise and summarise data before selecting statistical methods for proper interpretation.

MRCPUK-part-1-January 2019 exam: **A study is designed to assess the efficacy of a new antihypertensive drug. Two groups of patients are randomly assigned, one to take the established drug for 3 months whilst the other takes the new drug for 3 months. blood pressure is measured before and 3 months .After period off medication the drug swapped around and again, blood pressure is measured before and 3 months later. Which one of the following significance tests is it most appropriate to apply?**

→ Student's paired t-test (comparing parametric data from the same patients (they swapped medication halfway through the study))

Standard deviation

SD = square root (variance)

- **Remember that around two-thirds of values lie within 1 SD of the mean, one-third will therefore lie outside 1 SD, and half of these (one-sixth) will be less than 1 SD below the mean**

- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- **It is a measure of the spread of the sample distribution**
- SD = square root (variance)
- **The standard deviation** is a sort of average of the deviations of each observation from the mean, whereas **the range** is simply the difference between the largest and smallest observations.
- The standard deviation is affected by outliers and would be larger than expected if outliers are present
- If the data are skewed, the standard deviation will tend to overestimate the spread in the data
- If the standard deviation is reduced, the sample size required is smaller.
- **If SD increased the power of study is reduced .**
- **The standard deviation would give the best estimate of a spread of a measurement about the mean**
- Variance is the square of standard deviation. Standard deviation is the square root of variance.

Example How to Calculate Standard deviation (SD)

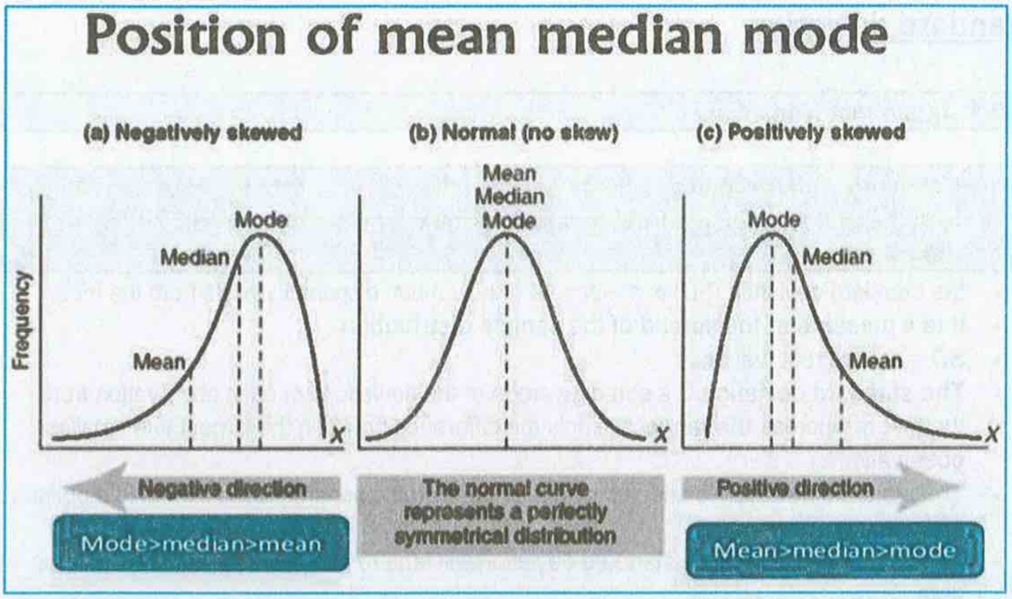
Dataset: 120, 125, 130 (e.g., systolic blood pressure in mmHg).

- **Step 1: Calculate the Mean** = (120+125+130) ÷ 3 =125
- **Step 2: Find the Squared Deviations** (the square of the difference between a data point and the mean):
  - For 120: (120 - 125)^2 = 25
  - For 125: (125 - 125)^2 = 0
  - For 130: (130 - 125)^2 = 25
- **Step 3: Calculate Variance** (the average of the squared deviations from the mean):
  - Variance = (25+0+25) ÷ 3 =16.67 (mmHg2)
- **Step 4: Take the Square Root of variance to get SD:**
  - SD=16.67=4.08 (mmHg)

Skewed distributions

- Alphabetical order: mean - median - mode
- '>' for positive skewed distribution , '<' for negative skewed distribution
  - Positively skewed distribution: mean > median > mode
  - Negatively skewed distribution mean < median < mode
  - To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'

Normal (Gaussian) distributions: mean = median = mode (bell-shaped)



Example: Mean, Median, Mode

Data: Blood sugar levels (in mmol/L): **3, 6, 1, 5, 5**

- **Mean (the average value of observations)** = summation of all numbers together dividing by the number of items.
  - **(3 + 6 + 1 + 5 + 5) ÷ 5 = 20/5 = 4**
- For the median and mode ➔ rewrite the values in ascending order: ie 1,1,**2**,3,4,
- **Median (the middle value when the values are placed in order) = 2**
  - ⇨ Rewrite the values in ascending order: 1, 3, 5, 5, 6 = **5**
  - ⇨ In a normal distribution the median equals the mean
  - ⇨ If the mean is greater than the median, this indicates a positive skew.
- **Mode (the most commonly observed value) = 5** (occurs twice, more than other values)

Confidence Interval (CI) and Standard Error of the Mean (SEM)

Confidence Interval (CI)

- **Definition:** A range of values within which the true value of a variable is likely to lie, with a specified probability called the confidence level.
  - **Confidence Limits:** The endpoints of the CI.
  - **Simplified Meaning:** A range where the true effect of an intervention is likely found.
- **Common Uses:** Applied to most statistical estimates (e.g., sensitivity or specificity of diagnostic tests).
- **95% Confidence Interval:**
  - **Meaning:** We are 95% confident that the true value lies within the range, with only a 5% chance that it is outside.
  - **Calculation:**
    - **Lower Limit:** Mean−(1.96 × SEM)
    - **Upper Limit:** Mean+(1.96 × SEM)

- **Significance:**
  - If the **95% CI does not include 0**, the difference is statistically significant ($p < 0.05$).
  - If the **95% CI includes 1**, the difference is **not statistically significant**, but this does not imply no effect.
- **Example:** Study Mean Height: 183 cm, SEM = 2
  - **95% CI:**
    - Lower limit: 183−(1.96×2) =179 cm.
    - Upper limit: 183+(1.96×2) =187 cm.
    - Interpretation: 95% chance the true mean lies between 179–187 cm.

Standard Error of the Mean (SEM):

- **Definition:** A measure of how much the sample mean is expected to vary from the true population mean.
- **Formula:** Calculated by dividing the standard deviation (SD) by the sample size's square root.
- **Key Features:**
  - SEM decreases as the sample size increases.
  - SEM is always smaller than the SD.
  - Reducing SEM narrows the CI, improving precision.

Assessment of Statistical Significance:

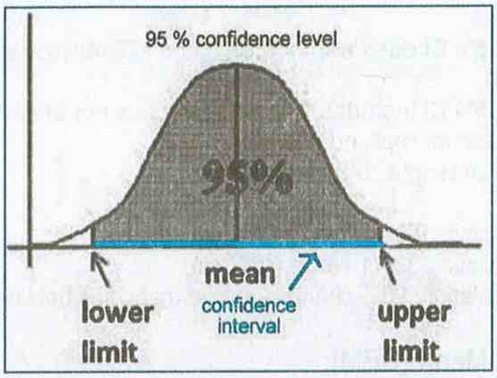
1. **Significant Results:**
   - $P < 0.05$: Statistically significant.
   - CI does not include 0 or 1.
   - Narrow CI increases confidence in results.
2. **Non-Significant Results:**
   - $P \geq 0.05$: Not statistically significant.
   - CI includes 0 or 1, suggesting insufficient evidence for a true difference.

Confidence Interval & Standard Error

Aspect	Definition/Key Features
Confidence Interval	A range where the true value is likely to lie with specified confidence.
95% CI	Contains the true value 95% of the time; calculated using SEM.
Significance	CI excluding 0 or 1 indicates statistical significance ($p<0.05$).
Standard Error (SEM)	Measures spread of sample mean from the true mean; decreases with larger sample size.

Standard error of the mean = standard deviation / square root (number of patients).
SEM = SD / square root (n). Where SD = standard deviation and n = sample size.

- **standard error of the mean gets smaller as the sample size increases**
- **Increasing the sample size will reduce the standard error of the mean and the width of the confidence interval.**
- **The standard error is smaller than the standard deviation.**



Screening test statistics

Sensitivity (True Positive Rate)

- **Definition:** The proportion of individuals with the disease who test positive.
- **Formula:** Sensitivity=True Positives (TP)/True Positives (TP)+False Negatives (FN)
- **Interpretation:** High sensitivity minimises false negatives.
- **Example:** A screening test for tuberculosis with 90% sensitivity detects 90% of individuals with the disease.

$$\text{Sensitivity} = \frac{\text{True Positives (TP)}}{\text{True Positives (TP)} + \text{False Negatives (FN)}}$$

Specificity (True Negative Rate)

- **Definition:** The proportion of individuals without the disease who test negative.
- **Formula:** Specificity=True Negatives (TN)/True Negatives (TN)+False Positives (FP)
- **Interpretation:** High specificity minimises false positives.
- **Example:** A screening test for breast cancer with 95% specificity correctly identifies 95% of individuals without the disease.

$$\text{Specificity} = \frac{\text{True Negatives (TN)}}{\text{True Negatives (TN)} + \text{False Positives (FP)}}$$

Positive Predictive Value (PPV)

- **Definition:** The proportion of positive test results that are true positives.
- **Formula:** PPV=True Positives (TP)/True Positives (TP)+False Positives (FP)

$$\text{PPV} = \frac{\text{True Positives (TP)}}{\text{True Positives (TP)} + \text{False Positives (FP)}}$$

- **Interpretation:** PPV depends on disease prevalence. Higher prevalence increases PPV.
- **Application:**
  - Used to determine the likelihood that a positive test result indicates the presence of a disease.
- **Advantages:**
  - Clinically useful in interpreting diagnostic test results.

- **Limitations:**
  - Highly dependent on disease prevalence; lower prevalence reduces PPV.
- **Example:**
  - A test identifies 80 true positives out of 100 positive results.
    PPV = 80 ÷ 100 = 80%.
  - A diabetes test with a PPV of 80% means 80% of positive results are true positives.

Negative Predictive Value (NPV)

- **Definition:** The proportion of negative test results that are true negatives.
- **Formula:** NPV=True Negatives (TN)/True Negatives (TN)+False Negatives (FN)

$$\text{NPV} = \frac{\textbf{True Negatives (TN)}}{\textbf{True Negatives (TN) + False Negatives (FN)}}$$

- **Interpretation:** NPV depends on disease prevalence. Lower prevalence increases NPV.
- **Application:**
  - Used to assess the likelihood that a negative test result indicates absence of disease.
- **Advantages:**
  - Useful in screening tests for ruling out conditions.
- **Limitations:**
  - Dependent on prevalence; higher prevalence reduces NPV.
- **Example:**
  - A test identifies 90 true negatives out of 100 negative results.
    NPV = 90 ÷ 100 = 90%.
  - An HIV test with a 98% NPV means 98% of negative results are true negatives.

Accuracy

- **Definition:** The proportion of correctly classified individuals (both true positives and true negatives).
- **Formula:**
  Accuracy=True Positives (TP)+True Negatives (TN)/Total Population (TP + TN + FP + FN)
- **Example:** A test with 90% accuracy correctly classifies 90% of all individuals tested.

$$\textbf{Accuracy} = \frac{\textbf{True Positives (TP) + True Negatives (TN)}}{\textbf{Total Population (TP + TN + FP + FN)}}$$

Likelihood Ratios

- **Positive Likelihood Ratio (LR+):** LR+=Sensitivity1−Specificity
  - Interpretation: Indicates how much a positive test result increases the likelihood of disease.

$$\text{LR+} = \frac{\textbf{Sensitivity}}{\textbf{1} - \textbf{Specificity}}$$

- **Negative Likelihood Ratio (LR-):** LR-=1−SensitivitySpecificity
  - Interpretation: Indicates how much a negative test result decreases the likelihood of disease.

$$\text{LR-} = \frac{\textbf{1} - \textbf{Sensitivity}}{\textbf{Specificity}}$$

- **Application:** Used in diagnostic tests to quantify how much a test result changes the probability of a disease.
- **Advantages:**
  - Independent of disease prevalence.
  - Combines sensitivity and specificity into a single measure.
- **Limitations:** Requires pre-test probability to calculate post-test probability.
- **Example:**
  - LR+ = Sensitivity ÷ (1 - Specificity).
    If sensitivity = 90% and specificity = 80%, LR+ = 0.9 ÷ (1 - 0.8) = 4.5 → A positive test increases disease odds by 4.5 times.

Prevalence

- **Definition:** The proportion of individuals in the population with the disease.
- **Formula:** Prevalence=True Positives (TP)+False Negatives (FN)/Total Population

$$\text{Prevalence} = \frac{\text{True Positives (TP)} + \text{False Negatives (FN)}}{\text{Total Population}}$$

Relative Risk (RR):

- **Definition:** Compares the risk of an outcome in the exposed group to the unexposed group.
- **Formula:** RR= Risk in exposed group ÷ Risk in unexposed group.

$$\text{RR} = \frac{\text{Risk in Exposed Group}}{\text{Risk in Unexposed Group}}$$

- Risk is calculated as the number of events (e.g., cases of disease) divided by the total number of individuals in the group. Formula: Number of events ÷ Total number in the group.
- **Interpretation:**
  - RR = 1: No difference in risk.
  - RR > 1: Increased risk in the exposed group.
  - RR < 1: Decreased risk in the exposed group.
- **For example:** If 20 out of 100 exposed individuals develop a disease, the risk in the exposed group is 20 ÷ 100 = 0.2 (20%). If 5 out of 100 unexposed individuals develop the disease, the risk in the unexposed group is 5 ÷ 100 = 0.05 (5%). Relative Risk = 0.2 ÷ 0.05 = 4. This means the exposed group has 4 times the risk of developing the disease compared to the unexposed group.
- **Application:**
  - Commonly used in **cohort studies**.
  - Assesses the impact of risk factors or interventions on disease occurrence.
- **Limitations:**
  - Cannot be used in case-control studies as incidence cannot be directly calculated. For such studies, **odds ratio** is used as an approximation.

Relative Risk Reduction (RRR)

- **Definition:**
  - Relative risk reduction quantifies the proportion by which the risk of an outcome is reduced in the intervention group compared to the control group.

- **Formula:**
  - **Relative risk reduction (RRR) or relative risk increase (RRI) is calculated by dividing the absolute risk change (**Experimental event rate (EER) - Control event rate (CER)**) by the control event rate.**
  - **Relative risk reduction = 1 − relative risk**
  - **The relative risk is always positive**

$$RRR = \left(\frac{\text{Risk in Control Group} - \text{Risk in Intervention Group}}{\text{Risk in Control Group}}\right) \times 100$$

Or equivalently:

$$RRR = (1 - \text{Relative Risk}) \times 100$$

- **Interpretation:**
  - **RRR** is expressed as a percentage and indicates the relative reduction in risk due to the intervention.
  - A higher RRR suggests a more effective intervention.
- **Example:**
  - Risk of disease in control group = 10% (0.10). Risk of disease in intervention group = 5% (0.05). RRR=0.10−0.050.10×100=50%
  - If a drug reduces the incidence of heart attacks from 12% to 8% then:
    - The control event rate (CER) is 12%
    - The experimental event rate (EER) is 8%
    - The relative risk reduction (RRR) is 33% ([EER-CER/CER] x 100)
    - The absolute risk reduction (ARR) is 4% (CER-EER)
    - The number needed to treat (NNT) is 25 ([1/ARR] x 100)

- **Interpretation:** The intervention reduces the relative risk of the disease by 50%.
- **Applications:**
  - Commonly used in clinical trials and epidemiological studies to compare treatment efficacy.
  - Helps convey the relative benefit of a new therapy.
- **Advantages:**
  - Useful for comparing interventions across studies.
  - Provides a straightforward measure of relative effectiveness.
- **Limitations:**
  - May be misleading if absolute risks are low.
  - Does not convey the absolute magnitude of the effect (absolute risk reduction or NNT is required for that).
- **Complementary Measures:**
  - **Absolute Risk Reduction (ARR):** Indicates the absolute difference in risk.
  - **Number Needed to Treat (NNT):** Practical measure of intervention benefit based on ARR.

Absolute Risk Reduction (ARR):

- **Definition:** The absolute difference in risk between two groups (e.g., intervention vs. control).
- **Formula:** ARR=Risk in Control Group−Risk in Intervention Group

$$\text{ARR} = \text{Risk in Control Group} - \text{Risk in Intervention Group}$$

- **Interpretation:** Indicates the number of events prevented by the intervention.
- **Application:**
  - Commonly used in cohort studies.
  - Assesses the impact of risk factors or interventions on disease occurrence.
- **Limitations:**
  - Cannot be used in case-control studies as incidence cannot be directly calculated. For such studies, odds ratio is used as an approximation.
- **Example:**
  - Risk of stroke with drug A = 5%; with placebo = 10%.
  - ARR = 10% - 5% = 5%.
  - This means drug A reduces stroke risk by 5%.

Numbers Needed to Treat (NNT):

- **Definition:** The number of patients that need to be treated to prevent one adverse event.
- **Formula:** NNT=1 / ARR

$$\text{NNT} = \frac{1}{\text{ARR}}$$

- **Interpretation:**
  - Lower NNT indicates a more effective intervention.
  - Example: NNT = 10 means treating 10 patients prevents 1 adverse event.
- **Application:**
  - Used in clinical decision-making to determine the practicality of an intervention.
- **Limitations:**
  - Depends on baseline risk; NNT may vary across populations.
  - Large NNT values may make the intervention clinically insignificant.
- **Example:**
  - ARR = 5%.
  - NNT = 1 ÷ 0.05 = 20.
  - This means 20 patients need to be treated to prevent 1 adverse event.

Odds:

- **Definition:** The ratio of the probability of an event occurring to the probability of it not occurring.
- **Formula:** Odds=Probability of Event1 - Probability of Event

$$\text{Odds} = \frac{\text{Probability of Event}}{\text{1 - Probability of Event}}$$

- **Example:** If the probability of disease is 0.2, the odds are 0.2/0.8=0.250.2 / 0.8 = 0.250.2/0.8=0.25.

Remember that risk and odds are different. If 20 patients die out of every 100 who have a myocardial infarction, then the risk of dying is 20 / 100 = 0.2 whereas the odds are 20 / 80 = 0.25.

Odds Ratio (OR):

- **Definition:** Compares the odds of an outcome in the exposed group to the unexposed group.
- **Formula:** OR = Odds in exposed group / odds in unexposed group

$$OR = \frac{\text{Odds in Exposed Group}}{\text{Odds in Unexposed Group}}$$

- **Interpretation:**
  - OR = 1: No difference in odds.
  - OR > 1: Higher odds in the exposed group.
  - OR < 1: Lower odds in the exposed group.
- **Application:**
  - Used in case-control studies to estimate the association between exposure and outcome.
- **Advantages:**
  - Applicable to retrospective studies.
  - A good estimate of RR in rare diseases.
- **Limitations:**
  - Can overestimate the risk in common conditions.
  - Harder to interpret than RR.
- **Example:**
  - In a case-control study, odds of smoking in lung cancer cases = 0.8; in controls = 0.2.
    OR = 0.8 ÷ 0.2 = 4 → Smokers have 4 times higher odds of lung cancer than non-smokers.
  - If we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

  - The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2
  - The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5
  - Therefore the odds ratio = 2 / 0.5 = 4

Probability:

- **Definition:** The likelihood of an event occurring.
- **Formula:** Probability = Favourable outcomes / Total Outcomes

$$\text{Probability} = \frac{\text{Favourable Outcomes}}{\text{Total Outcomes}}$$

- **Application:**
  - Measures the likelihood of an event occurring in various settings, including disease risk and outcomes.
- **Advantages:**
  - Simple to calculate and widely applicable.

- **Limitations:**
  - Does not quantify risk differences or relative associations.
- **Example:**
  - If 20 out of 100 patients have a disease, probability = 20 ÷ 100 = 0.2 or 20%.
  - If 30 out of 100 patients develop a condition, the probability is 0.3 or 30%.

Comparison of Relative Risk and Odds Ratio

Aspect	Relative Risk (RR)	Odds Ratio (OR)
Definition	Risk comparison between groups	Odds comparison between groups
Use	Cohort studies	Case-control studies
Range	0 to ∞	0 to ∞
Interpretation	Direct measure of risk	Estimate of risk in certain designs

Key Relationships

- Sensitivity and specificity are intrinsic to the test and independent of disease prevalence.
- PPV and NPV vary with disease prevalence.

Example Table (2x2 Contingency Table)

	Disease Present (D+)	Disease Absent (D−)
Test Positive	True Positive (TP)	False Positive (FP)
Test Negative	False Negative (FN)	True Negative (TN)

This table forms the basis for calculating all screening test statistics.

Clinical Application

- High **sensitivity** is critical for ruling out diseases (e.g., cancer screening).
- High **specificity** is important for confirming diseases (e.g., diagnostic tests for rare conditions).
- Likelihood ratios guide post-test probability assessments.

Sensitivity = true positives / (true positives + false negatives)

Specificity = true negatives / (true negatives + false positives)

The rule of thumb is that a high sensitivity helps to **rule out** disease (SnOut) and a high specificity helps to **rule in** (SpIn) disease (Mnemonic "spin and snout")

Absolute risk reduction = (Control event rate) - (Experimental event rate)

NNT= 1/absolute risk reduction

Odds
Remember a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome
NOT a ratio of the number of people who incur a particular outcome to the total number of people.

The table below lists the main statistical terms used in relation to screening tests:

Measure	Formula	Plain English
Sensitivity	TP / (TP + FN)	Proportion of patients with the condition who have a positive test result
Specificity	TN / (TN + FP)	Proportion of patients without the condition who have a negative test result
Positive predictive value	TP / (TP + FP)	The chance that the patient has the condition if the diagnostic test is positive
Negative predictive value	TN / (TN + FN)	The chance that the patient does not have the condition if the diagnostic test is negative
Likelihood ratio for a positive test result	sensitivity / (1 - specificity)	How much the odds of the disease increase when a test is positive
Likelihood ratio for a negative test result	(1 - sensitivity) / specificity	How much the odds of the disease decrease when a test is negative

Incidence and Prevalence

Incidence

- **Definition:** Measures the occurrence of new cases of a disease within a specified time period in a population at risk.
- **Formula:** Incidence Rate=number of new cases / population at risk × time Period

$$\text{Incidence Rate} = \frac{\text{Number of New Cases}}{\text{Population at Risk} \times \text{Time Period}}$$

- **Key Features:**
  - Focuses on new cases.
  - Indicates the risk of developing the disease.
  - Useful for studying disease causation and prevention.
- **Example:** If 50 people develop diabetes in a population of 1,000 over one year, the incidence rate is 50/1,000 = 5 per 1,000 per year.

Prevalence

- **Definition:** Measures the proportion of individuals in a population who have a disease at a specific point in time (point prevalence) or over a period of time (period prevalence).
- **Formula:** Prevalence = number of existing cases / total Population

$$\text{Prevalence} = \frac{\text{True Positives (TP)} + \text{False Negatives (FN)}}{\text{Total Population}}$$

- **Key Features:**
  - Includes both new and existing cases.
  - Indicates the burden of disease in a population.
  - Useful for resource allocation and health planning.
- **Example:** If 100 people in a population of 1,000 have diabetes at a specific time, the prevalence is 100/1,000 = 10%.

Key Differences:

Aspect	Incidence	Prevalence
Focus	New cases	All cases (new and existing)
Purpose	Measures risk	Measures disease burden
Denominator	Population at risk	Total population
Timeframe	Over a specific time period	At a specific point or period of time
Example	New cases of flu in a year	Total flu cases at a given point in time

Relationship Between Incidence and Prevalence:

- **Prevalence = incidence × average duration of disease**
- **Implication:** Prevalence increases with higher incidence or longer disease duration, and decreases with shorter disease duration or effective treatment/cure.
  - in chronic diseases the prevalence is much greater than the incidence
  - in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

Incidence is the number of new cases per population in a given time period.	**Prevalence** is the total number of cases per population at a particular point in time.

Scales of measurement

Data in medical studies can be categorised into one of four scales of measurement, each with specific properties and applications:

1. Nominal Scale

- **Description:** Data are categorised without any inherent order.
- **Examples:**
  - Blood groups (A, B, AB, O).
  - Gender (male, female).
  - Presence or absence of a disease (yes/no).
- **Properties:**
  - Categories are mutually exclusive.
  - No ranking or numerical value.
- **Statistical Use:** Frequencies, proportions, and mode.

2. Ordinal Scale

- **Description:** Data are categorised with a meaningful order but without consistent intervals between categories.
- **Examples:**
  - Pain severity (mild, moderate, severe).
  - Stages of cancer (Stage I, II, III, IV).
- **Properties:**
  - Categories can be ranked.
  - Intervals between ranks are not uniform.
- **Statistical Use:** Median, percentiles, and non-parametric tests.

3. Interval Scale

- **Description:** Data have ordered categories with equal intervals but no true zero point.
- **Examples:**
  - Temperature in Celsius or Fahrenheit.
  - IQ scores.
- **Properties:**
  - Allows addition and subtraction.
  - Ratios are not meaningful (e.g., 20°C is not twice as hot as 10°C).
- **Statistical Use:** Mean, standard deviation, and parametric tests.

4. Ratio Scale

- **Description:** Data have ordered categories with equal intervals and a true zero point.
- **Examples:**
  - Weight (kg).
  - Height (cm).
  - Blood pressure (mmHg).
- **Properties:**
  - Allows all arithmetic operations (addition, subtraction, multiplication, division).
  - Ratios are meaningful (e.g., 80kg is twice as heavy as 40kg).
- **Statistical Use:** Mean, standard deviation, and parametric tests.

Overview of Study designs

Definition

- Study design refers to the framework or methodology used to collect, measure, and analyse data in research. Selecting the appropriate study design is crucial for obtaining valid and reliable results.

Types of Study design

1. Observational Studies

These studies observe outcomes without intervention.

Type	Definition	Characteristics	Advantages	Disadvantages
Cross-sectional	Data collected at a single point in time.	Snapshot of a population, descriptive, evaluates prevalence.	Quick, inexpensive, good for hypothesis generation.	Cannot infer causality, prone to bias.
Case-control	Compares individuals with a condition (cases) to those without it (controls).	Retrospective, identifies potential risk factors.	Good for rare diseases, cost-effective, fast.	Recall bias, cannot estimate incidence.
Cohort	Follows a group over time to assess exposures and outcomes.	Prospective or retrospective, evaluates incidence and natural history.	Establishes temporal relationships, assesses multiple outcomes.	Expensive, time-consuming, risk of loss to follow-up.

2. Interventional (Experimental) Studies

These studies involve deliberate intervention to study effects.

Type	Definition	Characteristics	Advantages	Disadvantages
Randomised controlled trial (RCT)	Participants randomly assigned to intervention or control groups.	Gold standard for causality, includes blinding and randomisation.	Reduces bias, high-quality evidence, controls confounding factors.	Expensive, ethical constraints, may not reflect real-world settings.
Non-randomised trial	Participants allocated to intervention/control non-randomly.	Often used when randomisation is unethical.	Feasible in ethical constraints.	Higher risk of bias.

3. Descriptive Studies

These describe the occurrence of outcomes or exposures.

Type	Definition	Characteristics	Advantages	Disadvantages
Case report	Detailed report of a single patient or event.	Descriptive, highlights unique conditions or findings.	Generates hypotheses, educational.	Limited generalisability, no statistical analysis.
Case series	Collection of case reports.	Similar to case report, summarises multiple cases.	Hypothesis generation, informative.	No control group, prone to bias.

4. Analytical Studies

These analyse relationships between exposures and outcomes.

Type	Definition	Characteristics	Advantages	Disadvantages
Ecological study	Analyses data at the population level.	Examines correlations, uses existing datasets.	Quick, inexpensive, hypothesis generation.	Ecological fallacy, limited individual-level conclusions.

5. Systematic Reviews and Meta-analyses

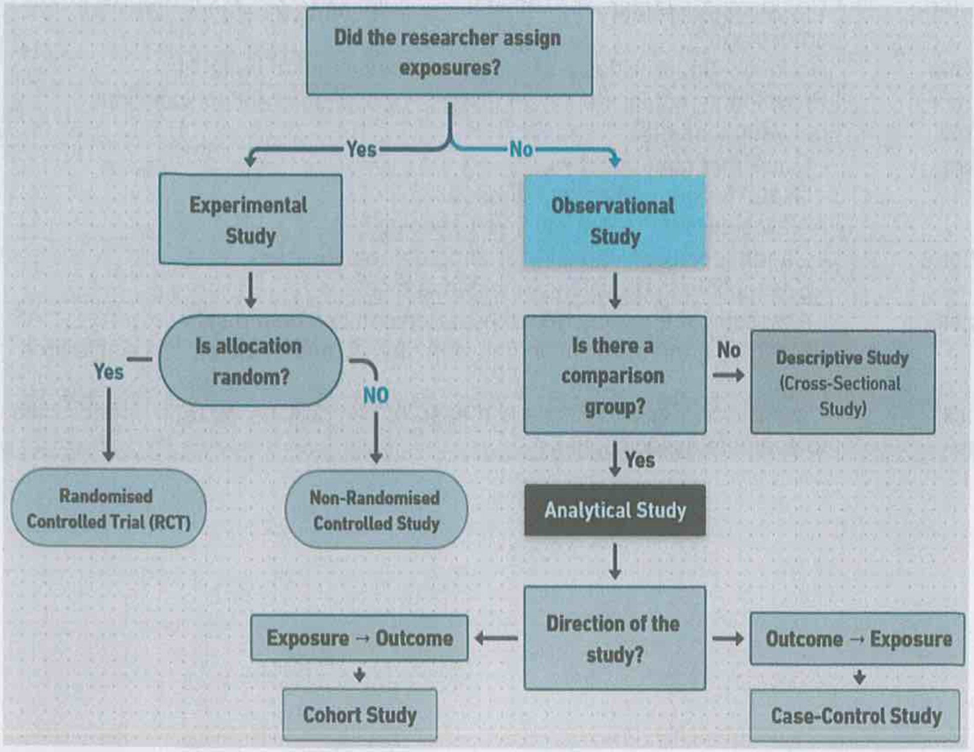
These synthesise data from multiple studies.

Type	Definition	Characteristics	Advantages	Disadvantages
Systematic review	Summarises evidence on a specific question systematically.	Predefined protocol, includes all relevant studies.	High-quality evidence synthesis.	Time-consuming, risk of publication bias.
Meta-analysis	Quantitative synthesis of pooled data from studies.	Statistical analysis of combined results.	Increases power and precision.	Heterogeneity between studies, publication bias.

Decision-making process for selecting a study design based on specific criteria:

1. **Start with the Research Question**:
   Determine if the researcher actively assigns the exposures (interventions) or simply observes them.
2. **If Exposures Are Assigned**:
   - This is an **Experimental Study**.
   - Assess if the allocation to groups is random:
     - **Yes**: Choose a **Randomised Controlled Trial (RCT)**, which is the gold standard for causality.
     - **No**: Choose a **Non-Randomised Controlled Study**, often used when randomisation is impractical or unethical.
3. **If Exposures Are Not Assigned**:
   - This is an **Observational Study**.
   - Determine if there is a comparison group:
     - **Yes**: Proceed with an **Analytical Study**. Evaluate the direction of the study:
       - **Forward in time (Exposure → Outcome)**: Choose a **Cohort Study**.
       - **Backward in time (Outcome → Exposure)**: Choose a **Case-Control Study**.
     - **No**: Choose a **Descriptive Study**, such as a **Cross-Sectional Study**, which captures data on exposure and outcome simultaneously.

How to select study design?



Select Study Design to Match the Research Goals

Objective	Study design
Describe of disease or spectrum	Case series or report Cross sectional study
Determine operating characteristics of a new diagnostic test	Cross sectional study
Describe prognosis	Cohort study
Determine cause-effect	Cohort study Case control study
Compare new interventions	Randomised clinical trial
summarize literature	Meta-analysis

Cross-Sectional Study

Feature	Description
Definition	An observational study that collects data at a single point in time to assess the prevalence of outcomes or exposures.
Objective	To describe the distribution of disease, conditions, or risk factors in a specific population.
Design	Data on exposure and outcome are collected simultaneously in a "snapshot" format.
Population	A sample of individuals from a target population, often selected randomly to represent the group.
Comparison	Can compare subgroups within the population (e.g., smokers vs non-smokers).
Timeframe	No follow-up; provides a single-time assessment of variables.
Outcomes Measured	Prevalence (not incidence) of disease or exposure and associations between variables.
Strengths	- Quick and cost-effective. - Useful for generating hypotheses. - Allows assessment of multiple variables.
Limitations	- Cannot establish causality or temporal relationships. - Susceptible to prevalence-incidence bias.
Examples	- Assessing the prevalence of hypertension in a community. - Evaluating the association between obesity and diabetes at a single time point.
Statistical Analysis	Uses descriptive statistics and measures like prevalence ratio or odds ratio to evaluate associations.

Randomised Controlled Trial (RCT)

Feature	Description
Definition	A study where participants are randomly assigned to intervention or control groups to evaluate a treatment's effect.
Objective	To determine the causal relationship between an intervention and an outcome.
Randomisation	Ensures participants are allocated to groups by chance, reducing selection bias.
Control Group	Provides a baseline for comparison (e.g., placebo or standard treatment group).
Blinding	Can be single-blind (participants unaware) or double-blind (participants and researchers unaware) to minimise bias.
Intervention	Deliberate application of treatment, procedure, or exposure under controlled conditions.
Outcomes Measured	Primary (main effect) and secondary (additional effects) outcomes predefined in the study protocol.
Strengths	- Reduces bias. - Establishes causation. - High internal validity.
Limitations	- Expensive and resource-intensive. - May be ethically challenging. - May lack generalisability.
Examples	Trials of new medications, vaccines, surgical interventions, or lifestyle changes (e.g., dietary interventions).
Statistical Analysis	Uses intention-to-treat analysis to preserve randomisation and minimise bias.

The purpose of randomisation is to prevent systematic differences (bias) between treatment groups.

Methods of Analysis for RCTs

1. **Intention-to-Treat (ITT) Analysis**
    - **Definition**: Analyses all randomised participants in their assigned groups, regardless of adherence.
    - **Advantages**: Preserves randomisation, reduces bias, and reflects real-world effectiveness.
    - **Limitations**: Effect may be diluted by non-compliance or missing data.
2. **Per-Protocol Analysis**
    - **Definition**: Includes only participants who strictly followed the protocol and completed the intervention.
    - **Advantages**: Measures efficacy under ideal conditions.

Intention-to-Treat (ITT) Analysis ensures all randomised participants are analysed in their assigned groups, Including the patients who drop out in the final data set. preserving randomisation and reducing bias, making it the gold standard for evaluating real-world effectiveness.

Cohort Study

Feature	Description
Definition	An observational study that follows a group (cohort) over time to assess the relationship between exposures and outcomes.
Objective	To study the incidence, causes, and natural progression of a condition or disease.
Design	Can be **prospective** (data collected in real-time) or **retrospective** (data obtained from historical records).
Population	Participants are selected based on exposure status and followed to observe outcomes.
Comparison	Compares exposed and unexposed groups to evaluate the effect of exposure on outcomes.
Timeframe	Requires long-term follow-up for prospective studies; retrospective studies rely on existing data.
Outcomes Measured	Incidence of disease, relative risk (RR), and risk factors associated with exposure.
Strengths	- Can establish temporal relationships. - Suitable for rare exposures. - Allows analysis of multiple outcomes.
Limitations	- Expensive and time-consuming (for prospective studies). - Risk of loss to follow-up. - Susceptible to confounding.
Examples	- Studying the impact of smoking on lung cancer development. - Analysing the long-term effects of occupational exposures.
Statistical Analysis	Uses measures such as relative risk (RR), attributable risk, and survival analysis to assess outcomes.

Types of Cohort Studies

1. **Prospective Cohort Study**
   - **Description**: Study begins before the outcome develops.
   - **Exposure**: Participants are categorised as exposed or unexposed to a risk factor.
   - **Outcome**: Participants are followed prospectively to observe differences in outcome rates.
   - **Example**: Smokers and non-smokers are followed over time to compare lung cancer rates.
2. **Retrospective Cohort Study**
   - **Description**: Study begins after both exposure and outcome have occurred.
   - **Exposure**: Participants are categorised based on past exposure to a risk factor.
   - **Outcome**: Previously collected data is analysed to compare outcome rates.
   - **Example**: Historical data on smokers and non-smokers from 5 years ago is analysed to compare lung cancer rates.

In **cohort studies**, the study **sample is selected based on exposure to a risk factor**.

In case-control studies, the study **sample is selected according to having a disease or not**, and then it is determined which participants were exposed to a risk factor.

Case-Control Study

Feature	Description
Definition	An observational study that compares individuals with a specific outcome (cases) to those without the outcome (controls) to assess exposure.
Objective	To identify and quantify associations between exposures and outcomes, often for rare diseases.
Design	Retrospective; starts with the outcome and looks backward to identify exposure history.
Population	Cases: Individuals with the disease/outcome. Controls: Individuals without the disease/outcome but otherwise similar.
Comparison	Compares the frequency of exposures in cases versus controls to identify potential risk factors.
Timeframe	Relies on past exposure data, which may involve medical records, interviews, or questionnaires.
Outcomes Measured	Odds ratio (OR) is calculated to estimate the association between exposure and outcome.
Strengths	- Suitable for studying rare diseases. - Quick and cost-effective. - Requires fewer participants.
Limitations	- Prone to recall bias (participants' memory of exposures). - Cannot determine causality. - Selection bias in control group choice.
Examples	- Studying the association between asbestos exposure and mesothelioma. - Investigating dietary habits in individuals with and without colorectal cancer.
Statistical Analysis	Primarily calculates odds ratios to evaluate the strength of associations.

In Cohort study: The usual outcome measure is the relative risk.

In Case-control study: The usual outcome measure is the odds ratio.

A case-control study generally examines a **small population** group over a **short period of time** (**less cost-intensive**) and evaluates the **association between multiple exposures and one outcome. Can be used to study rare diseases.**

A cohort study generally examines a **large population** over a **long period of time** (**more cost-intensive**) and determines **how one exposure is associated with multiple outcomes**.

Systematic Review and Meta-Analysis

Feature	Systematic Review	Meta-Analysis
Definition	A comprehensive summary of existing studies addressing a specific research question using a standardised methodology.	A statistical technique that combines results from multiple studies to produce a single quantitative estimate.
Objective	To synthesise evidence systematically to address a research question.	To increase statistical power and precision by pooling data from multiple studies.
Design	Follows a predefined protocol, including systematic literature search, study selection, and data extraction.	Quantitative synthesis of data extracted in a systematic review, using statistical tools to summarise findings.
Population	Includes all relevant studies on a specific topic (e.g., RCTs, observational studies).	Requires comparable studies with similar methodologies and outcomes.
Comparison	Compares and contrasts methodologies, findings, and quality of included studies.	Provides pooled effect sizes (e.g., relative risk, odds ratio) to compare interventions or associations.
Timeframe	Depends on the scope of the research question and available data.	Requires sufficient studies with consistent data to conduct meaningful analysis.
Outcomes Measured	Summarises qualitative findings, methodological quality, and consistency of results.	Produces a single pooled effect estimate and may assess heterogeneity using metrics like I^2.
Strengths	- High-quality evidence synthesis. - Reduces bias via rigorous methodology.	- Improves statistical power. - Resolves inconsistencies across studies.
Limitations	- Time-consuming. - Publication bias may affect findings.	- Subject to heterogeneity among studies. - Dependent on quality of included studies.
Examples	- Reviewing the efficacy of COVID-19 vaccines across published trials.	- Pooling data to quantify the risk reduction of stroke with antihypertensive therapy.
Statistical Analysis	Descriptive summary of included studies.	Uses statistical methods like fixed-effects or random-effects models to combine data.

Funnel plots - show publication bias in meta-analyses

Meta-analysis

Definition: Meta-analysis combines systematic reviews with quantitative measures.
Primary Use: Commonly used in treatment studies.
Process: Combines all previous data, offering rapid and efficient results.
Evidence Level: Produces the highest level of evidence.
Publication Bias: Positive results are published more frequently than negative ones, potentially leading to bias.
Weighting: Each study's weight is proportional to its sample size.
Funnel Plot: Used to detect publication bias in meta-analyses.
Forest Plot: The best graphical representation of meta-analysis results

Common Biases in Studies

Recall Bias:

- **Definition:** Participants remember exposures differently based on their outcome status.
- **Occurs In:** Case-control studies.
- **Prevention:** Use objective measures of exposure (e.g., medical records) and standardised, validated questionnaires.
- **Example:** In a study on lung cancer, cases may overreport past smoking compared to controls due to the belief that smoking caused their disease.

Selection Bias:

- **Definition:** Participants are not representative of the target population.
- **Occurs In:** All study designs, especially observational studies.
- **Prevention:** Use random sampling or randomisation, and establish rigorous inclusion and exclusion criteria.
- **Example:** A study on hypertension excludes individuals who work night shifts, leading to non-representative findings.

Attrition Bias:

- **Definition:** Unequal loss of participants between study groups skews results.
- **Occurs In:** Longitudinal studies and RCTs.
- **Prevention:** Minimise dropouts through regular follow-ups and analyse data using intention-to-treat methods.
- **Example:** In a weight loss study, participants in the intervention group drop out more frequently due to side effects of the treatment.

Information Bias:

- **Definition:** Inaccurate measurement or classification of variables.
- **Occurs In:** Observational studies and surveys.
- **Prevention:** Use validated tools, standardised protocols, and train data collectors to ensure accuracy.
- **Example:** A survey on alcohol consumption relies on self-reports, which may underestimate intake due to underreporting.

Performance Bias:

- **Definition:** Participants or researchers behave differently due to knowledge of group assignment.
- **Occurs In:** Interventional studies.
- **Prevention:** Use single or double blinding to minimise awareness of group assignments.
- **Example:** In a trial of a new pain medication, participants in the active group report better outcomes due to their belief that they are receiving the effective treatment.

Detection Bias:

- **Definition:** Outcome detection differs between groups due to knowledge of intervention.
- **Occurs In:** RCTs and observational studies.
- **Prevention:** Use blinding and consistent outcome assessment protocols for all groups.
- **Example:** Researchers evaluating a cancer therapy focus more closely on detecting recurrences in the experimental group.

Confounding:

- **Definition:** An extraneous variable is associated with both the exposure and the outcome, distorting the relationship.
- **Occurs In:** Observational studies.
- **Prevention:**
  - Use randomisation, matching, or statistical adjustments (e.g., multivariable regression models).
  - **A randomised controlled trial eliminates confounding**
  - **Stratified analysis eliminates the confounding** (dividing the data into subgroups (strata) based on a confounding or other characteristic. Each subgroup is analysed separately to account for confounding or to explore specific patterns within strata.).
- **Example:**
  - A study finds that coffee consumption is associated with heart disease, but the true confounder is smoking, which is more prevalent among coffee drinkers.
  - In a case-control study on the association between cola drinking and type 2 diabetes → **BMI is likely to be a confounding variable**

Publication Bias:

- **Definition:** Positive or significant results are more likely to be published than null findings.
- **Occurs In:** Systematic reviews and meta-analyses.
- **Prevention:** Register trials prospectively (e.g., clinical trial registries) and include grey literature in comprehensive searches.
- **Example:** A meta-analysis of antidepressants includes only published trials, which overestimate the efficacy of the drugs.

Hawthorne Effect:

- **Definition:** Participants alter their behaviour because they are being observed.
- **Occurs In:** Behavioural studies.
- **Prevention:** Minimise participants' awareness of being studied (if ethical) and maintain consistent study conditions.
- **Example:** Workers in a factory improve productivity during a study on working conditions because they know they are being monitored.

Social Desirability Bias:

- **Definition:** Participants provide socially acceptable rather than truthful responses.
- **Occurs In:** Surveys and interviews.
- **Prevention:** Use anonymous data collection methods and validate responses with objective measures where possible.
- **Example:** In a dietary survey, participants underreport unhealthy food consumption to appear healthier.

Ecological Fallacy:

- **Definition:** Misinterpretation of group-level data when applied to individuals.
- **Occurs In:** Ecological studies.
- **Prevention:** Avoid drawing conclusions about individuals from group-level data and conduct individual-level analyses when possible.
- **Example:** A study shows a higher incidence of lung cancer in regions with high pollution, but the conclusion cannot be applied to individuals without considering smoking or other factors.

Types of Trials

1. **Randomised Controlled Trial (RCT)**
   - Participants are randomly allocated to intervention or control groups.
   - *Purpose*: Test efficacy and causality of treatments or interventions.
   - *Example*: Comparing a new drug to a placebo.
2. **Non-Randomised Controlled Trial**
   - Participants are assigned to groups without randomisation.
   - *Purpose*: Used when randomisation is impractical or unethical.
   - *Example*: Comparing outcomes between hospitals with different policies.
3. **Blinded Trials**
   - **Single-Blind**: Participants are unaware of their group allocation.
   - **Double-Blind**: Both participants and researchers are unaware of group allocation.
   - *Purpose*: Minimise bias.
4. **Crossover Trial**
   - Participants receive multiple treatments sequentially, acting as their own controls.
   - *Purpose*: Compare treatments while controlling individual variability.
   - *Example*: Testing two blood pressure medications in the same group.
5. **Cluster Randomised Trial**
   - Groups (e.g., schools, hospitals) are randomised instead of individuals.
   - *Purpose*: Evaluate interventions applied at the group level.
   - *Example*: Testing a vaccination programme in schools.
6. **Pragmatic Trial**
   - Conducted in real-world settings to test intervention effectiveness.
   - *Purpose*: Reflect practical application.
   - *Example*: Testing a diabetes management programme in primary care.
7. **Adaptive Trial**
   - Design allows modifications based on interim results.
   - *Purpose*: Increase efficiency and flexibility.
   - *Example*: Stopping ineffective treatments early.
8. **Equivalence/Non-Inferiority Trials**
   - Test if a new intervention is equivalent or not worse than an existing one.
   - *Purpose*: Compare alternatives.
   - *Example*: Evaluating a generic drug vs a branded drug.
9. **Pilot Trial**
   - Small-scale preliminary study to assess feasibility.
   - *Purpose*: Refine study design.
   - *Example*: Testing recruitment strategies for a large RCT.

Study design: evidence and recommendations

Study Design: Evidence and Recommendations

The strength of Evidence

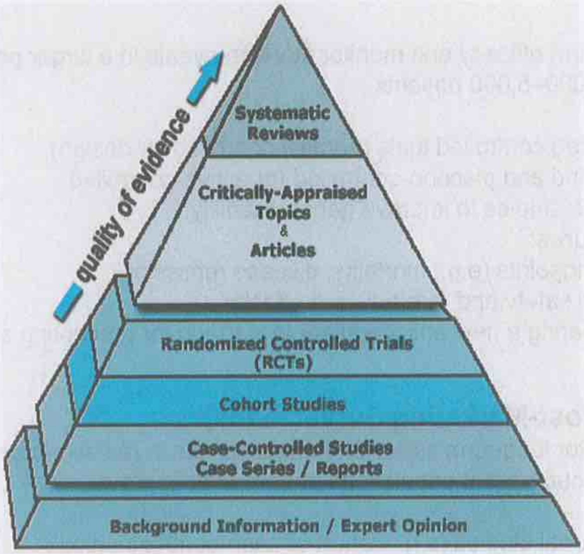
1. **Systematic Reviews and Meta-Analyses**
    - **Strength:** Highest level of evidence.
    - **Description:** Combines results from multiple studies to provide a comprehensive summary.
    - **Use:** Establishes clinical guidelines and recommendations.
2. **Randomised Controlled Trials (RCTs)**
    - **Strength:** Gold standard for assessing interventions.
    - **Description:** Participants are randomly allocated to intervention or control groups.
    - **Use:** Evaluates efficacy, safety, and causality.
3. **Cohort Studies**
    - **Strength:** High for determining associations.
    - **Description:** Follows groups with and without exposures over time.
    - **Use:** Observes long-term outcomes (e.g., risk factors for disease).
4. **Case-Control Studies**
    - **Strength:** Moderate.
    - **Description:** Compares patients with a condition (cases) to those without it (controls).
    - **Use:** Identifies associations and potential risk factors.
5. **Cross-Sectional Studies**
    - **Strength:** Moderate to low.
    - **Description:** Analyses data at a single point in time.
    - **Use:** Determines prevalence and identifies correlations.
6. **Case Reports and Case Series**
    - **Strength:** Low.
    - **Description:** Detailed observations of single or multiple cases.
    - **Use:** Generates hypotheses and highlights rare conditions.
7. **Expert Opinion**
    - **Strength:** Lowest level of evidence.
    - **Description:** Based on clinical experience or theoretical knowledge.
    - **Use:** Used when higher levels of evidence are unavailable.

Grading of Recommendations Based on Evidence

1. **Grade A (Strong Recommendation):**
    - Supported by high-quality evidence (e.g., multiple RCTs, systematic reviews).
    - Examples: Use of statins to reduce cardiovascular risk in patients with hyperlipidaemia.
2. **Grade B (Moderate Recommendation):**
    - Based on moderate-quality evidence (e.g., cohort studies or RCTs with limitations).
    - Examples: Screening for diabetes in high-risk populations.
3. **Grade C (Weak Recommendation):**
    - Based on low-quality evidence or expert opinion.
    - Examples: Use of novel treatments for rare diseases without extensive trials.
4. **Grade D (Insufficient Evidence):**
    - Evidence is insufficient to recommend for or against the intervention.
    - Examples: Experimental therapies or treatments with limited data.

Levels of evidence

- Ia - evidence from meta-analysis of randomised controlled trials
- Ib - evidence from at least one randomised controlled trial
- IIa - evidence from at least one well designed controlled trial which is not randomised
- IIb - evidence from at least one well designed experimental trial
- III - evidence from case, correlation and comparative studies
- IV - evidence from a panel of experts



Study Design for New Drug Evaluation

Preclinical Studies:

- **Objective:** Assess safety, toxicity, and pharmacokinetics in laboratory and animal models.
- **Study Type:** Non-human laboratory studies.
- **Example:** Testing the cytotoxicity of a new cancer drug in cultured tumour cells.

Phase 1 Studies:

- **Objective:** Evaluate safety, dosage, and pharmacokinetics in humans.
- **Participants:** 20–100 healthy volunteers or patients (for toxic drugs like chemotherapy).
- **Study Design:**
  - Open-label or non-randomised.
  - Dose-escalation studies (to determine maximum tolerated dose).
- **Outcome Measures:**
  - Adverse effects.
  - Pharmacokinetic parameters (e.g., half-life, bioavailability).
- **Example:** Testing a new antihypertensive drug for tolerability at escalating doses.

Phase 2 Studies:

- **Objective:** Assess efficacy and safety in a small patient population.
- **Participants:** 100–300 patients with the target condition.

- **Study Design:**
  - Randomised controlled trial (RCT) or single-arm study.
  - Often double-blinded.
- **Outcome Measures:**
  - Preliminary efficacy (e.g., reduction in blood pressure).
  - Side effects and safety profile.
- **Example:** Evaluating the efficacy of a novel diabetes drug in lowering HbA1c levels compared to placebo.

Phase 3 Studies:

- **Objective:** Confirm efficacy and monitor adverse events in a larger population.
- **Participants:** 1,000–5,000 patients.
- **Study Design:**
  - Randomised controlled trials (parallel or crossover design).
  - Double-blind and placebo-controlled (or active-controlled).
  - Multicentre studies to improve generalisability.
- **Outcome Measures:**
  - Clinical endpoints (e.g., mortality, disease remission).
  - Long-term safety and rare adverse effects.
- **Example:** Comparing a new anticoagulant to warfarin for preventing stroke in atrial fibrillation.

Phase 4 Studies (Post-Marketing Surveillance):

- **Objective:** Monitor long-term safety and effectiveness in real-world settings.
- **Participants:** Broad patient populations after market approval.
- **Study Design:**
  - Observational studies (e.g., cohort or case-control studies).
  - Registry studies or database analyses.
- **Outcome Measures:**
  - Long-term adverse effects.
  - Drug-drug interactions.
  - Real-world effectiveness.
- **Example:** Monitoring the risk of myocardial infarction with a newly marketed non-steroidal anti-inflammatory drug.

Study Design Options

1. **Placebo-Controlled Trial:**
   - Provides robust evidence but may be unethical if established treatments are available.
   - Does not compare the new drug to standard treatments.
2. **Comparison to Existing Treatment:**
   - **Superiority:**
     - Aim: Show the new drug is better than the existing treatment.
     - Challenge: Requires large sample sizes to demonstrate significant benefits.
   - **Equivalence:**
     - Aim: Demonstrate the new drug has a similar effect to the standard treatment.
     - Method: Define an equivalence margin (-delta to +delta) for outcomes. If the confidence interval falls within this range, equivalence is confirmed.

- **Non-Inferiority:**
  - Aim: Show the new drug is not worse than the standard treatment by more than a specified margin.
  - Method: Only the lower confidence interval must fall within the equivalence margin (-delta).
  - Advantage: Requires smaller sample sizes than superiority trials.
  - Further Studies: After proving non-inferiority, larger trials may be conducted to establish superiority.
- **Drug Companies' Perspective:** Demonstrating equivalence or non-inferiority may suffice for marketing advantages such as price or convenience.

Phases of New Drug Development

Phase	Goal	Notes
Animal Trials	Assess safety for human testing	Preclinical studies.
Phase I	Initial safety and metabolism	Conducted in 20–80 healthy volunteers. Identifies common side effects and drug metabolism.
Phase II	Effectiveness (RCTs)	Includes 30–300 patients. Tests efficacy and short-term safety.
Phase III	Comparative efficacy	Involves 300–3,000 patients. Best design is a randomised controlled trial. Compares new drug with standard treatments.
Phase IV (Post-Marketing)	Detect long-term side effects	Enrolls thousands of patients. Observes real-world effectiveness and rare adverse events.

Superiority trial ➔ a large sample size is required to demonstrate a significant difference